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METASTATIC MALIGNANT MELANOMA
DIAGNOSIS AND THERAPY

A clinical study



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The present thesis is based on the following papers:

- I. G Agrup, P Agrup, T Andersson, Lo Hafström, C Hansson, S Jacobsson, P-E Jönsson, H Rorsman, A-M Rosengren and E Rosengren. 5 YEARS' EXPERIENCE OF 5-S-CYSTEINYLDOPA IN MELANOMA DIAGNOSIS. Acta Dermatovener (Stockholm) 59:381-388, 1979.
- II. P-E Jönsson, G Agrup, E Arnbjörnsson, Lo Hafström and H Rorsman. TREATMENT OF MALIGNANT MELANOMA WITH DACARBAZIN (DTIC-DOME) WITH SPECIAL REFERENCE TO URINARY EXCRETION OF 5-S-CYSTEINYLDOPA. Cancer 45:245-248, 1980.
- III. Lo Hafström, P-E Jönsson and L-G Strömblad. INTRACRANIAL METASTASES OF MALIGNANT MELANOMA TREATED BY SURGERY. Accepted for publication in Cancer, 1979.
- IV. P-E Jönsson, S-E Strand, L Bergqvist, S Dawiskiba, Lo Hafström and BRR Persson. QUANTITATIVE LYMPHOSCINTIGRAPHY II: IMAGING TECHNIQUE, DOSIMETRY AND HISTOPATHOLOGY IN PATIENTS WITH MALIGNANT MELANOMA. Submitted for publication in J. Nucl. Med., 1980.
- V. Lo Hafström and P-E Jönsson. HYPERTHERMIC PERFUSION OF ADVANCED MALIGNANT MELANOMA ON THE EXTREMITIES. Accepted for publication in Acta Chir. Scand., 1980.
- VI. Lo Hafström, A Hugander, P-E Jönsson and L-G Lindberg. ASPIRATION FINE NEEDLE CYTODIAGNOSIS OF RECURRENT MALIGNANT MELANOMA. Accepted for publication in J. Surg. Oncol., 1979.

The papers will be referred to by their Roman numerals, I-VI.

INTRODUCTION

Malignant melanoma originates in the melanocyte, a pigment-producing cell in the epidermis. Skin melanoma as a clinical entity dates back as far as to Hippocrates (Urteaga and Pack 1956). Sir James Paget estimated in 1864, that all malignant melanoma arose in or under a benign naevus (Paget 1864). Not until 1882, when Hutchinson described the melanotic freckle, was it realized that pigmented lesions could appear during adult life and give rise to melanoma (Hutchinson 1882). It is impossible to determine the proportion of malignant melanoma that have developed from pre-existent naevi, but nearly two thirds of patients with malignant melanoma have a history of pre-existent pigmented lesion (Milton 1972).

Incidence and mortality

Malignant melanoma, the most malignant of skin tumors, is an uncommon tumor constituting less than 2 % of all malignant tumors registered in Sweden each year (Cancer Incidence in Sweden 1973). There has been a true incidence increase in this country during recent years. The incidence increase for malignant melanoma was 69 % whereas it was no more than 28 % for all other malignant tumors during the period 1959-1961 compared with 1966-1968. (Malec and Eklund 1978).

Melanoma occurs in all the human populations which have been studied. There is varying incidence among sexes, ages and tumor sites (Elwood and Lee 1975, Malec and Eklund 1978). The highest incidence rate is observed among white people all over the world (Crombie 1979).

In Sweden the melanoma annual incidence rate per 100 000 individuals increased from 2.9 to 5.2 for men and 3.3 to 6.0 for women during 1959-1968 (Malec and Eklund 1978). The incidence during this period was somewhat higher for women than for men. The tumor site distribution differed between the sexes. The highest incidence for men being found on the trunk and for women on the lower extremities. For both men and women the greatest annual percentage increase was in tumors on the trunk.

The Scandinavian countries have the highest mortality rate from malignant melanoma in Europe (Elwood and Lee 1975). In Sweden the mean mortality rate for men was 2.05 compared with 1.05 for women per 100 000 individuals during 1959-1968 (Malec and Eklund 1978). In other countries the mortality rate varies from 0.2 in Japan and Hongkong to 5-6 per 100 000 individuals in Australia and New Zealand (Cutler and Young 1975). There have been conflicting reports about increased or not increased mortality rates in Sweden (Ericsson and Ringertz 1972, Malec and Eklund 1978), probably due to differences in the time periods investigated. The Swedish Cancer Registry gives information about the mortality rate up to 1973 and there is a tendency to a small increase (Cancer Incidence in Sweden 1973). Remarkable is the inversed relationship between mortality and incidence in both sexes; the incidence is higher in women while the mortality is higher in men (Malec and Eklund 1978).

Ethiological aspects

The exposure of ultraviolet light on the skin is considered to be one of the possible causes for the increase in the incidence of and mortality from malignant melanoma (Emmet 1973). Even if epidemiological studies imply a more complex ethiology, sunlight has been considered of particular importance because of the inversed relationship between melanoma incidence and latitudes (Lancaster 1956, Elwood et al 1974). Such a correlation has been found also in Sweden (Eklund and Malec 1978).

Other factors such as racial or familial indicate a possible genetic control of malignant melanoma (Wallace et al 1971, Lynch et al 1977, Anaise et al 1978). Multiple primary melanoma in familial cases is reported to be as frequent as 25 % (Anderson et al 1967). In non-familial malignant melanoma, about 5 % of those patients with one diagnosed primary melanoma develop further primary tumors (Vaisman et al 1979). The risk of developing a second primary melanoma in these cases is calculated to be about 900 times greater than the risk of developing a primary melanoma in the general population (Veronesi et al 1976). There are reports that malignant melanoma occurs more frequently in red-haired people exposed to excessive sunlight (Lancaster 1956, Magnus 1973). 5-S-cysteinyl-dopa, one of the compounds forming the red pigment, has been shown to be excreted in greater amounts after sun exposure in the urine of red-haired people indicating increased sensitivity of the melanocytes to sunlight in these people (Rorsman et al 1979).

Prognostic factors

General factors which influence the prognosis are age, sex and tumor site. Patients younger than 45 years at the time of diagnosis of primary malignant melanoma have a better 5-year survival than those older than 45 years, and women have better prognosis than men (Mastrangelo et al 1979). Patients with melanoma localized on the lower extremities have the best survival rate, worst when on the trunk and intermediate when on the head and neck (Vaisman et al 1979). This may be an explanation for the differences in survival time between sexes as primary melanoma of the lower extremities is more common in women than in men (Malec and Eklund 1978). Of great importance is the biological behaviour of the melanoma tumor. Table I shows an example of different clinical features which have been combined with a prognostic score (Mackie et al 1972).

Since Clark defined the relationship between the infiltration level of the primary tumor and Breslow between the tumor thickness of the primary tumor and prognosis (Clark et al 1969, Breslow 1970) it has been easier to differentiate the treatment of patients with primary melanoma. It has been found that the single, most important determinant for clinical stage I disease is the maximum tumor thickness, however, both classifications complement each other in some cases (Breslow et al 1978, Balch et al 1979).

Spread of the tumor beyond the level of the primary tumor determines the prognosis for the patient (DeVita and Fisher 1976). In patients with

Table I. Prognostic score sheet according to Mackie et al 1972.

Clinical features	Score
Sex	
female	1
male	6
Site	
head and neck	1
lower limb	3
trunk	6
upper limb	2
anogenital	6
subungual	4
mucosal	8
occult	8
Size	
less than 2 cm diameter	1
2 cm or larger diameter	4
Duration of symptoms	
less than 2 years	1
2 years or more	2
Exposed site	1
Nonexposed site	5
Nodal involvement	
no	1
yes	10
Disseminated disease	15

a primary tumor classified according to Clark's levels IV and V there is a probability of regional lymph node metastases occurring in as many as 20-50 % when there are clinically uninvolved lymph nodes (Wanebo et al 1975, Breslow 1975, Fortner et al 1977, Breslow et al 1978). When evaluating different series of malignant melanoma it is important to know both the classification of the primary tumor and the classification according to clinical stage. Examples of the most used clinical classifications are shown in Table II.

Table II.

Clinical staging system	
Stage I	Stage I
local disease	local disease
	Stage II
	local recurrence; within or adjacent to the scar of the primary lesion
Stage II	Stage III A
regional nodal disease	regional metastases, in transit disease or satellitosis
	Stage III B
	regional node disease
Stage III	Stage III AB
disseminated disease	regional metastases and regional node disease
	Stage IV
	disseminated disease

Development of metastatic disease

The prognosis is poor for patients with metastatic malignant melanoma. Very little is known about the further development of the disease when metastases are manifest. Malignant melanoma can metastasize to any anatomic site of the body (Das Gupta and Brasfield 1964, Einhorn et al 1974). Apart from regional metastases, it is very difficult to predict to which organ the tumor will metastasize. Most information about metastatic spread is received from autopsy series (Das Gupta and Brasfield 1964, Einhorn et al 1974). DeVita et al have reported on a natural history of patients with primary melanoma treated by surgery (Fig 1) (DeVita and Fisher 1976). The figures of other series may differ from these as the population of primarily treated patients varies.

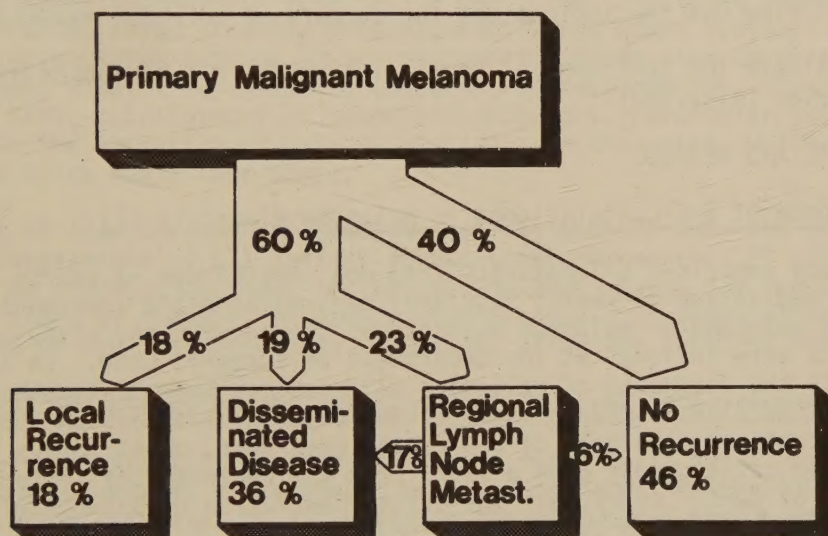


Fig 1. Natural history of cutaneous malignant melanoma treated by surgery.

The metastatic site influences the prognosis so a careful assessment of patients is important before any treatment is begun. Patients with metastases localized to the skin, subcutaneous and lymph node tissues and lungs have a far better prognosis than patients with metastases in other organs. The outlook for patients with liver or cerebral metastases is considered practically hopeless.

THE AIM OF THE PRESENT STUDY

This study has been focused on diagnostic and therapeutic procedures in metastatic malignant melanoma. The purpose has been to:

- 1) estimate the value of the urinary excretion of 5-S-cysteinyl-dopa as an indicator of tumor progression and prognosis,
- 2) develop a scintillation camera technique for investigation of lymph drainage and lymph nodes,
- 3) determine the value of percutaneous fine needle aspiration biopsies in patients with suspected recurrent melanoma,
- 4) evaluate the therapeutic effect of dacarbazin (DTIC-DOME^R) with special reference to the urinary excretion of 5-S-cysteinyl-dopa,
- 5) evaluate the value of surgical resection for cerebral metastases and find out the indications for surgery of cerebral metastases, and
- 6) evaluate the treatment of regional hyperthermic perfusion with melphalan (Alkeran^R).

MATERIAL AND METHODS

Experience of 5-S-cysteinyl-dopa in melanoma diagnosis (I).

The study comprises 571 patients (243 men, median age 57 years, 328 women, median age 63 years) regularly controlled after treatment of primary melanoma or melanoma metastases. One hundred and sixty of these patients were followed at the department of surgery, Lund. In all patients the diagnosis of malignant melanoma has been histopathologically verified. The follow-up has included physical examination and laboratory tests at intervals of 3-4 months each year, chest X-rays twice and liver scintigraphy once a year. From the beginning of September to the end of April every year the urinary excretion of 5-S-cysteinyl-dopa was estimated at each clinical control.

For the determination of 5-S-cysteinyl-dopa, 24-hour urinary output was collected in plastic bottles containing 50 ml acetic acid and 1 g sodium metabisulfite. Twenty ml of the collected urine was absorbed to aluminiumoxide and diluted with 1.1 % hydrochloric acid. A fluorimetric method was used for determination of the 5-S-cysteinyl-dopa (Rorsman et al 1973). Values below 0.15 mg/24 hours are considered normal, values between 0.15 and 0.40 mg/24 hours are borderline and above 0.40 mg/24 hours are pathological values.

Treatment of malignant melanoma with dacarbazin with special reference to urinary excretion of 5-S-cysteinyl-dopa (II).

Seventeen patients (nine men, eight women, age range 40-74 years) were

treated by systemic administration of dacarbazin. Four patients were also given regional intraarterial infusion; one patient in the hepatic artery, one in the gastroduodenal artery and two in the external iliac artery. Four patients with lymph node metastases surgically removed at the time of the primary tumor were treated adjuvantly. Thirteen patients were treated because of recurrent tumor. Before the administration of dacarbazin all patients with resectable tumors had these removed by surgery. Four patients with massive tumor growth in the specimen after axillary dissection received radiotherapy before the chemotherapeutic treatment was started.

The standard dose schedule of dacarbazin was 200 mg/m²/day intravenously for five days at intervals of 4-6 weeks. All 17 patients were given at least three courses of this regimen. The same amount of dacarbazin was given by intraarterial infusion but at intervals of 3-5 weeks.

The effect of the treatment was checked by regular clinical controls, laboratory tests (hemoglobin rate, white cell count, platelet count, serum bilirubin, serum alkaline phosphatases, serum gamma glutamyl transpeptidase, serum aspartate amino transferase, serum alanine amino transferase), chest X-ray or chest tomogram, ultrasonography, liver scintigraphy, brain scintigraphy or computer tomography. Particular attention was paid to the excretion of 5-S-cysteinyldopa in the urine, which was determined twice every four weeks.

The effect of chemotherapy was evaluated as follows: 1) complete regression - disappearance of all lesions for at least two months; 2) stable disease - no increase of known lesions and no new lesions for two months after the start of therapy; 3) progressive disease - increase of known lesions and/or new lesions within two months after the start of therapy.

Intracranial metastases of malignant melanoma treated by surgery (III).

Twenty-five patients (15 men, ten women, age range 31-75 years) with intracranial metastases of malignant melanoma operated in 1968-1978 were analysed retrospectively. In all patients the metastases have been proved histologically to be malignant melanoma. The primary melanoma was recognized in 18 patients, 16 before and two after the brain surgery. In ten patients the brain metastases were the first manifestation of the melanoma tumor after primary treatment. At the time for neurosurgery seven patients had concomitant metastases on other sites and eight patients had had extracranial metastases surgically removed earlier.

Craniotomy was performed and the metastases extirpated in all 25 patients. In one of them in combination with a Spitz-Holter shunt. A second craniotomy was performed in two patients because of intracranial tumor recurrence. In connection with the brain surgery all patients received corticosteroids. Chemotherapy was given to two patients before and two patients after neurosurgery because of extracranial metastases. One patient was given radiotherapy postoperatively.

Quantitative lymphoscintigraphy in patients with malignant melanoma (IV).

Five patients with melanoma on the trunk and four with melanoma on the lower extremities were examined by scintillation camera technique. Technetium-99-m-antimony sulphide colloid was injected subcutaneously. The injection site was around the scar of the excision of the primary lesion for patients with melanoma on the trunk and on the back of the foot for patients with melanoma on the lower extremities (fig 7). As a control, an identical injection procedure was performed in the contralateral side of the body at the same time for seven patients and four weeks later for two patients.

The first two hours after the injection sequential images were taken every 15 sec of patients with melanoma on the lower extremities. After 4-6 hours static images were taken of all patients. Lymph node dissection was performed the following day and the specimen was measured for radioactivity and examined by light microscopy.

The activity content of the lymph nodes was measured (in vitro) with an automatic sample changer NaI(Tl) (Sodiumiodide (Thallium activated)) well-counter. The activity uptake in the lymph nodes was calculated by comparing the count rate from the nodes with a standard prepared from the Technetium-99-m colloid vial used for the injection.

In the specimens from five patients each lymph node was isolated, weighed and inserted into separate plastic test tubes with fixative and the activity content was individually measured. Later on each lymph node was sectioned and stained with hematoxylin-erythrosine before examination by light microscopy.

The quantitative activity uptake in the areas of lymph nodes seen in the camera images was calculated from the net number of counts $N(t)$ in a region of interest with background activity subtracted. Using the known calibration factor $\alpha(d)$ for the scintillation camera, i.e., the count rate per unit of activity for the actual depth d of the lymph nodes (Aspegren et al 1978) and the injected activity $A(0)$, the percentage uptake $P(t)$ in each lymph node area, the time t after the injection was calculated according to

$$P(t) = \frac{N(t)}{\alpha(d) \cdot A(0)} \cdot e^{\lambda t}$$

The depth d of the lymph nodes was estimated either from anterior-posterior measurements or from lateral views (Aspegren et al 1978, Strand 1979).

The absorbed dose to the injection site and to individual lymph nodes was calculated according to the recommendations of the MIRD committee and/or using a computer program for internal dosimetry (MIRD 1968 and 1971, Grönberg et al 1977). The actual measured uptake values and weights for the lymph nodes were used.

Regional hyperthermic perfusion (V).

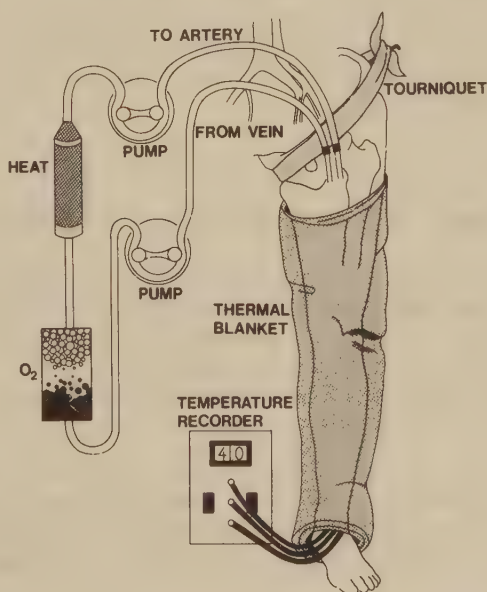
Twenty-one patients (seven men, 14 women, age range 46-78 years, median age 64 years) with recurrent melanoma on the extremities were treated by regional hyperthermic perfusion with melphalan. Four patients had a second perfusion because of further recurrences five to 19 months after the initial procedure. The diagnosis of recurrent melanoma was verified histopathologically or cytologically in all 21 patients. The indications for regional perfusion were local recurrences or regional metastases (in transit metastases) distal to the upper third of the upper and lower extremities with or without regional lymph node metastases.

The pretreatment evaluation included physical examination, laboratory tests (hemoglobin rate, white cell count, platelet count, serum bilirubin, serum alkaline phosphatases, serum gamma glutamyl transpeptidase, serum aspartate amino transferase, serum alanine amino transferase and 5-S-cysteinyldopa in the urine) and chest X-ray in all 21 patients. Liver scintigraphy was performed in 19 patients, brain scintigraphy or computer tomography of the brain in 13 patients. After the perfusion treatment, regular clinical controls were carried out with laboratory tests, chest X-ray and liver scintigraphy. When any signs of neurological symptoms appeared brain scintigraphy or computer tomography were added.

In patients with manifest tumor, tumor response was evaluated by regular clinical examination and by histopathological examination after delayed excision.

The perfusion technique used was that presented by others (Stehlin et al 1975) (Fig 2).

Fig 2. Schematic view of technique for regional perfusion of lower extremity with cytostatics and controlled hyperthermia. The extremity is isolated with a heating mattress. Thermistor probes are inserted for continuous registration of the temperature in the extremity.



The temperature (40-41°C i.m.) of the extremity was registered continuously during the perfusion which lasted two hours. Melphalan was used in a dose of 0.9 mg/kg bodyweight for lower extremity perfusion and 0.45 mg/kg bodyweight for upper extremity perfusion.

Regional lymph node dissection was performed in all patients. Eleven patients had the recurrent melanoma tumor excised before the perfusion treatment. Eight patients who had not had these tumors excised before, had a delayed excision 4-6 weeks after the perfusion treatment. In patients with in transit metastases only occasional lesions were excised surgically. Eight patients with systemic metastases after the perfusion treatment were given dacarbazine either by systemic administration or by regional intraarterial infusion.

Cytodiagnosis of recurrent malignant melanoma (VI).

Sixty-four patients with malignant melanoma were fine needle biopsied on suspicion of recurrent tumor. Eighty-four biopsies were aspirated percutaneously and three at exploratory laparotomy. A tumor mass was palpated when 81 of these biopsies were taken. The remaining biopsies were taken with the guidance of liver scintigraphy or fluoroscopy.

A 10 ml disposable plastic syringe fitted in to an adaptor permitting single-handed manipulation was used (CAMECO Ltd, Enebyberg, Sweden). A needle attached to the syringe had an outer diameter of 0.6-0.8 mm and a length varying from 25-80 mm. During maximum aspiration the needle was moved quickly back and forth in the lesion.

A sufficient volume of fluid was aspirated to fill no more than the needle lumen and the aspiration was discontinued before the needle was withdrawn from the lesion. The aspirated fluid was smeared on one or two glass slides which were then immediately fixed (before air-drying) in 95 % ethanol and stained with hematoxylin-erythrosine. A preliminary report was available as early as 10-15 min after the aspiration had been performed.

RESULTS

Experience of 5-S-cysteinyldopa in melanoma diagnosis (I).

During the observation period 161 patients of 571 (95 men and 66 women) exhibited melanoma metastases. The distribution of 5-S-cysteinyldopa excretion values in patients with and without metastases is evident from Table III (the highest value obtained is reported). The 5-S-cysteinyldopa excretion values reach higher levels in men with metastases than in women.

Nineteen patients out of these 161 had normal 5-S-cysteinyldopa excretion in the urine at the time when the metastases were first detected. The metastases in these 19 patients were amelanotic or weakly pigmented, solitary and/or small, but some cases had even pigmented numerous metastases.

Table III. Distribution of 5-S-cysteinyldopa excretion values in patients with and without metastases.

5-S-cysteinyldopa/ urine (mg/24 h)	Metastases		No metastases	
	m	f	m	f
Pathological > 0.4	63	32	3	3
Borderline 0.15-0.4	30	19	15	6
Normal < 0.15	2	15	130	253

Twenty-three patients (12 men and 11 women) with no symptoms or clinical signs of metastases had elevated 5-S-cysteinyldopa excretion giving rise to investigations leading to detection of metastases within 0.5-14 months). Twelve out of these 23 patients had borderline values. The metastatic sites were lymph nodes in five patients, liver metastases in one patient, lung metastases in two, brain metastases in three and skeleton metastases in one patient.

In 22 patients (16 men and six women) history and clinical examination including other diagnostic procedures motivated 5-S-cysteinyldopa determination and the results confirmed the suspicion of melanoma metastases. In seven out of these 22 patients there was unknown primary melanoma. 5-S-cysteinyldopa was useful in predicting the prognosis of patients with metastases which is illustrated in Table IV.

Table IV. Survival time in 154 patients with metastases at different 5-S-cysteinyldopa excretion values.

5-S-cysteinyldopa/ urine (mg/24 h)	> one month (%)	> one year (%)
< 0.15	94	50
0.15-0.40	91	42
0.40-1.0	84	16
1.0-5.0	76	9
> 5.0	56	3

Treatment of malignant melanoma with dacarbazine with special reference to urinary excretion of 5-S-cysteinyldopa (II).

Tumor response, tumor recurrence and survival time are shown in Table V for patients treated adjuvantly and in Table VI for patients treated palliatively.

Patient Sex Age (years)	5-S-cysteinyl dopa/urine			Tumor recurrence after start of therapy		Survival after start of therapy (months)	
	Before start of therapy	During therapy	Time of change after start of therapy (months)	Site	Time (months)	Alive	Dead
F 72	(+)	(+)		Brain	6		8
M 50	n	n				12	
M 48	n	+	1	Liver	4		5
F 60	n	(+)	3	Lymph nodes	7	15	

n = normal value, 0-150 $\mu\text{g}/24\text{ h}$

+ = increased value, > 400 $\mu\text{g}/24\text{ h}$

(+) = borderline value, 150-400 $\mu\text{g}/24\text{ h}$

Table V.

Patient Sex Age (years)	Tumor response	5-S-cysteinyl dopa/urine			Tumor recurrence after start of therapy		Survival after start of therapy (months)	
		Before therapy	During therapy	Time of change after start of therapy (months)	Site	Time (months)	Alive	Dead
M 66	Complete regression	+	n	2	Subcutis	2.5	19	
F 51	Stable disease	n	n	-	Lungs ^x	8.1 ^x		14
F 68	Stable disease	n	+	4	Brain ^x	9 ^x		11
M 53	Stable disease	+	++	1	Liver ^x	8 ^x	15	
M 74	Stable disease	n	(+)	2	Liver ^x	4 ^x		5
M 46	Stable disease	n	+	1	Lungs, liver ^x	3 ^x	20	
M 46	Stable disease	(+)	+	1	Brain ^x	3 ^x		3
M 47	Progressive disease	n	+	0.5	Lymph nodes	1.5		5
F 60	Progressive disease	n	+	1	Subcutis, liver	1.5		5
F 59	Progressive disease	(+)	++	1	Pancreas	1		5
F 70	Progressive disease	+	+	1	Subcutis, liver	1.5		6
M 40	Progressive disease	n	+	1	Lungs	1.5		8
F 55	Progressive disease	n	(+)	1	Lymph nodes	1		5

n = normal value, 0-150 $\mu\text{g}/24\text{ h}$

(+) = borderline value, 150-400 $\mu\text{g}/24\text{ h}$

+ = increased value, > 400 $\mu\text{g}/24\text{ h}$

++ = massively increased value, > 5000 $\mu\text{g}/24\text{ h}$

^x = Time and site for progression after period of stable disease.

Table VI.

The 5-S-cysteinyl dopa excretion in urine was raised before the metastasis was clinically detected in ten patients. The relationship of 5-S-cysteinyl dopa before and during therapy and time of change after start of therapy are shown in Table V and VI.

Two patients had leucopenia and one had thrombocytopenia. Gastrointestinal discomfort such as nausea and vomiting were common and occurred in 13 out of 17 patients who were given dacarbazin systemically. Only one of four patients receiving dacarbazin by intraarterial infusion experienced slight gastrointestinal disturbances. Thrombophlebitis was observed after intravenous administration in four patients. Intraarterial infusion caused no vascular complications, except for minor asymptomatic

brachial artery thrombosis caused by the catheter. Erythema and flushing was seen in one patient. Three patients had neurological signs, headache, a slight expressive aphasia and hemiparesis respectively. In these patients brain metastases were revealed one week and two and three months later, respectively.

Intracranial metastases of malignant melanoma treated by surgery (III).

Single metastases were found in 20 patients and multiple in five patients. The most frequent location of the metastases was in the parietal lobes with no hemispherical dominance. The time interval between the primary melanoma diagnosis and that of the intracranial metastases varied from 17 years to six months before the brain surgery. Preoperatively the intracranial tumors were localized by angiography in all 25 patients, by brain scintigraphy in 20 out of 21 patients and by computer tomography in four out of four patients.

Seven patients died within one month postoperatively. Three patients died from postoperative complications (septicemia, intracranial hematoma, pulmonary embolus) and four patients from tumor progress (multiple brain metastases). The median survival time of all patients was five months (mean survival time ten months). When one month mortality was deducted the median survival time was six months (mean survival time 13 months). Five of these patients are still alive, one after 12 months with extracranial recurrences and four without any signs of recurrent disease after 11, 21, 45 and 74 months respectively. The median survival time of patients with concomitant extracranial metastases was one month (mean survival time 2.5 months) to be compared with five months (mean survival 15 months) for patients without extracranial metastases. No differences in survival time were seen between patients with extracranial metastases treated earlier than those with no metastases. Patients with an unknown or known primary tumor had the same survival time. Patients with a long interval between the primary tumor and brain metastases had a better survival time than those with a short interval.

An immediate improvement with relief from symptoms was seen in 19 patients, complete in 17 and partial in two. The median duration of this improvement was five months (mean time 12 months) and median survival time of these patients was six months (mean survival time 15 months). Both the patients operated on a second time had also on this occasion complete relief from symptoms. All patients surviving one month or more had after surgery the same or improved quality of life. Fourteen of them went back to their ordinary occupation.

One patient had septicemia and one a wound abscess postoperatively. Intracerebral hematoma occurred in two patients, one of them died of this complication while the other was reoperated successfully. One patient died of pulmonary embolus.

Quantitative lymphoscintigraphy in patients with malignant melanoma

(IV).

The lymphatic drainage of Technetium-99-m-colloid from the injection site to regional lymph nodes was shown in all nine patients. In two of five patients with trunk melanoma lymph flow to more than one group of regional lymph nodes was demonstrated. Most of the uptake of activity in lymph nodes could be seen within the first 15 min. In three patients a reduced activity uptake was found, which was correlated to histopathological findings of metastases in one patient (Fig 3 a). A normal lymphoscintigraphy is shown in Fig 3 b.

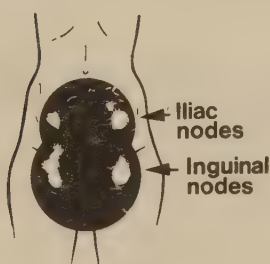


Fig 3 a. Pathological activity uptake with a more rapid uptake in the metastatic side whereas the total uptake after 5 hours shows reduced uptake in the metastatic side.

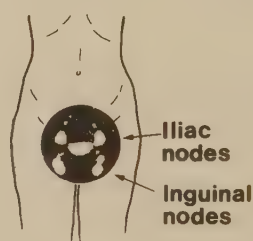
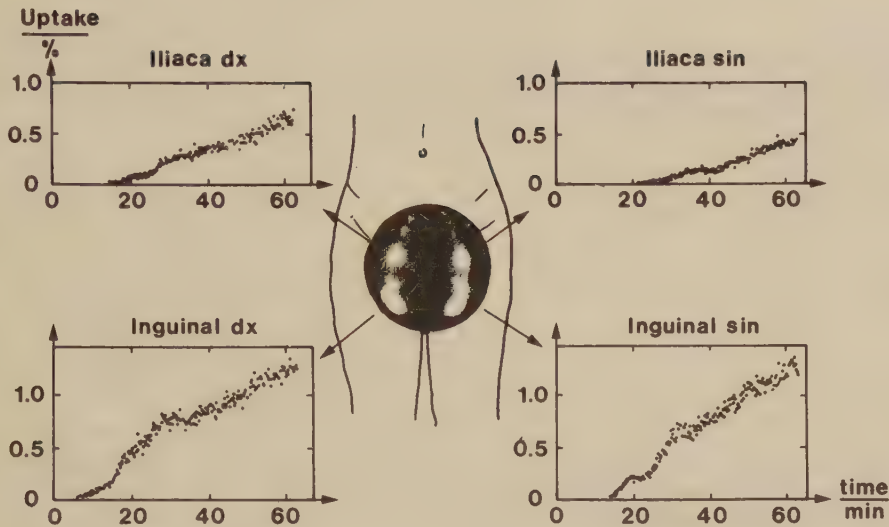


Fig 3 b. Normal activity uptake with no difference contralaterally.

A total of 74 lymph nodes were dissected from the specimens from five patients. Tumor growth was found in 5/74 lymph nodes. Activity uptake was detected in none of the lymph nodes infiltrated with melanoma but in 50 of the benign lymph nodes.

An example of a dynamic study is given in Fig 4. The scintillation camera measurements give the total activity content in the regional lymph nodes examined. The variation of activity uptake is great and ranges up to 5 %. The remaining activity to the injection sites ranges from 80-100 % after about 5 hours.

There was no significant activity (< 0.001 %) in any of the metastatic lymph nodes and in 28 % of the benign lymph nodes. In the remaining benign lymph nodes the most probably activity content was between 0.001-0.01 % in 30 % and 0.01-0.1 % in 33 % of the nodes. The activity content rarely exceeded 0.1 % and only 9 % of the benign lymph nodes had an activity content between 0.1-1 %. The mean weight of the 69 lymph nodes was 0.7 g.



Colloid uptake in lymph nodes

Fig 4. Time activity curves of the inguinal and iliacal lymph nodes. The more rapid uptake in the inguinal lymph nodes is due to the shorter distance to the injection site.

The absorbed dose to the injection site and to individual lymph nodes are given in Fig 5 a och 5 b. The absorbed dose is reduced when the volume of the injected activity is increased. The absorbed dose to the gonads is shown both from the MIRD and the computer calculations to be between 10-15 mrad per mCi ($2.7\text{--}4.1\text{ }\mu\text{Gy}$ per MBq) injected into the abdomen and 0.7 mrad per mCi ($0.19\text{ }\mu\text{Gy}$ per MBq) when injected into the foot.

Fig 5 a. The absorbed dose to the injection site for different volumes on the injection sites. Curves are given for the injected activity of 1 mCi for 2 extremes, when all the activities remain in the injection site and when only 80 % of the activity remains after 8 hours.

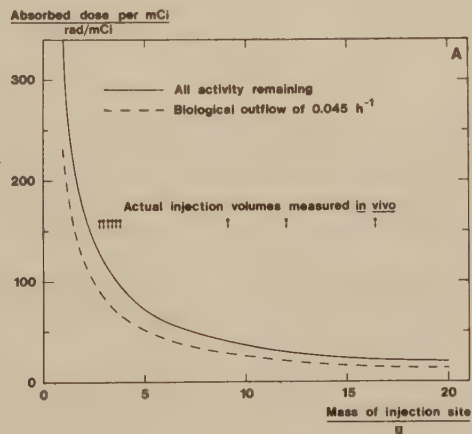
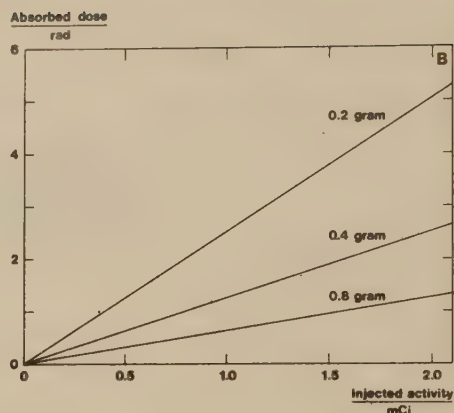


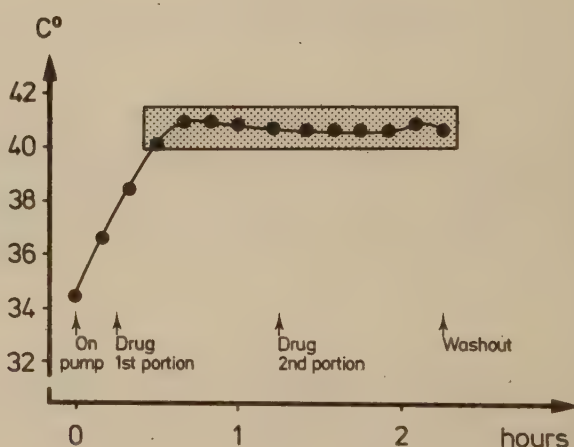
Fig 5 b. The absorbed doses to individual lymph nodes with the weights 0.2, 0.4 and 0.8 grammes when the uptake of injected activity is 0.1 %.



Regional hyperthermic perfusion (V).

The temperature curve during a regional perfusion with controlled hyperthermia is shown in Fig 6.

Fig 6. Temperature registered before and during perfusion. Dotted area indicates period for hyperthermia.



In ten patients with manifest tumor at the time for perfusion treatment the tumor response was as follows; one patient had total tumor regression and seven more than 50 % tumor regression, one patient had less than 50 % tumor regression and one patient demonstrated no response.

The relation between the site of the perfused recurrence and the clinical stage related to further recurrences after the treatment is shown in Table VII. Four patients had a local recurrence on the perfused limb as the first manifestation of tumor progress. In three of these patients it was the only manifestation of the disease. A further three patients with local recurrences had distant metastases at the same time. Ten patients had systemic metastases as the first sign of recurrence. One of these developed regional metastases later on. The median time after perfusion

	Upper part of of the limb	Lower part of the limb	Foot
The localization of the treated recurrence	6 (1)	13	1
Positive regional lymph nodes	5 (0)	6	0
Localization of the first recurrences after the perfusion			
Local	0	7	0
Distant	5 (1)	2	0

Table VII. The results of perfusion treatment with reference to regional lymph node dissection and recurrence site. All are related to the site on the extremity of the tumor which was treated. Figures in parentheses indicate the upper extremity perfusion.

for a new local recurrence was eight months (range 1-20 months) and for systemic recurrences seven months (range 4-39 months). Of the four patients reperfused three are still alive, one with a surgically excised local recurrence 20 months after the second perfusion. One patient has died from brain metastases three months after the reperfusion. One patient died one month after the perfusion. Postmortem examination showed cerebral haemorrhage but no signs of malignant melanoma. Further ten patients died 6.5-36 months after the perfusion (median time 17 months). Four patients are alive with recurrent disease after 11, 16, 43 and 44 months, respectively. Six patients have no signs of recurrent disease and are alive after 5.5, 6.5, 16, 21, 28 and 43 months, respectively.

No toxic effects on bone marrow have been registered. There was a third degree burn caused by a heat lamp in one patient. The injury was excised, covered with split skin grafts and healed uneventfully. Wound infection was seen in four patients, hematoma in five and seroma in eight.

Cytodiagnosis of recurrent malignant melanoma (VI).

The cytodiagnosis was malignant melanoma in 45 biopsies, malignant mesenchymal tumor in one and breast cancer in one. Forty of the biopsies were normal. The diagnosis of malignant melanoma was verified histopathologically in 37 of the 45 patients with the cytodiagnosis malignant melanoma. The remaining eight patients had typical tumors excised with a macroscopical appearance of malignant melanoma. The diagnoses of breast cancer and malignant mesenchymal tumor were revised to malignant melanoma after histopathological examination. Both these tumors were amelanotic.

Of the 40 normal biopsies the diagnoses were revised in three. Two of these patients had liver metastases and one a pancreatic metastasis. No patients with regional metastases or lymph node metastases had any false negative cytodiagnoses. There were no false positive diagnoses and the frequency of false negative diagnoses was only 6 %.

No patient suffered any discomfort during the aspiration procedure and no complications were revealed afterwards.

DISCUSSION

Purpose of diagnosis

The aim of the preoperative evaluation of patients with malignant melanoma is to determine whether metastases are present. This knowledge is important for planning the therapy. In treating melanoma patients, not only surgery, but also other therapeutic modalities as chemotherapy, immunotherapy and radiotherapy have to be considered (Hersh et al 1979). A correct pre-evaluation is important to avoid unnecessary treatment. In the follow-up an early diagnosis of recurrences might institute therapeutic possibilities, which could be of temporary or permanent benefit for the patient. Chemotherapy may imply a risk for the patient when there are metastases not diagnosed, for example neurological symptoms from occult brain metastases can be initiated by chemotherapy (Hafström and Jönsson 1980).

The diagnostic procedures routinely used for melanoma patients are various laboratory tests, chest X-ray including chest tomogram, and liver scintigraphy (Meyer and Stolbachi 1978, Gromet et al 1979). At some clinics, brain and bone scintigraphy have been used routinely (Einhorn et al 1974, Roth et al 1975, Aranha et al 1979). Ultrasonography and computer tomography have been reported to be valuable for staging melanoma patients and for evaluating the effects of different treatments (Bernardino and Goldstein 1978). Lymphography and various radionuclide techniques for the investigation of the lymphatic system have been used with varying results (Cox et al 1966, Musumeci et al 1976, Fee et al 1978, Meyer et al 1979). It is impossible to compare and evaluate the results of different series of patients, because the populations to which the diagnostic procedures have been applied are not sufficiently defined regarding clinical stage and other prognostic factors. When many diagnostic methods are available, it is important to know which method should be used, when and why. The risks with the method used in relation to the diagnostic and therapeutic exchange for the patient have also to be carefully considered, as well as the economical aspects.

Lymph node metastases

Microstaging of primary melanoma according to Clark and Breslow has shown that this has a close correlation with the occurrence of occult lymph node metastases (Clark et al 1969, Breslow 1970, Breslow 1975, Wanebo et al 1975, Breslow et al 1978). When regional lymph nodes are clinically involved all physicians agree on their surgical removal. There are still, however, great controversies about whether or not to perform prophylactical lymph node dissection in patients with clinically uninvolved lymph nodes (Goldsmith et al 1970, McCarthy et al 1974, Southwick 1976, DasGupta 1976, Holmes et al 1977, Fortner et al 1977, Veronesi et al 1977, Sim et al 1978). When there is minor enlargement of regional lymph

nodes it is impossible to determine if they are benign or not. The usual approach to these patients has been to take excision biopsies or to perform an immediate lymph node dissection. The high diagnostic accuracy of fine needle biopsy established in patients with lymph node metastases makes this method preferable to diagnostic surgical excision biopsy or lymph node dissection (VI). Unnecessary lymph node dissection should be avoided as it leads to significant morbidity, e.g., seroma, wound infection, flap necrosis and lymph oedema (Harris et al 1973, McCarthy et al 1974, Holmes et al 1977). This is quite the contrary to the consequences of fine needle biopsy of regional lymph nodes (VI). Any conclusion about the accuracy of fine needle biopsy technique in predicting occult lymph node metastases cannot be drawn from the present series because of the high prevalence of lymph node metastases (VI). An advantage of the fine needle biopsy technique is that it can be combined with non-invasive diagnostic methods such as ultrasonography and computer tomography (Hancke et al 1975, Alfidi and Haagar 1976). The biopsy can by these methods be directed to the visualized pathological changes.

Patients with melanoma of the lower extremity and with regional inguinal lymph node metastases have in some percentage further tumor growth in the aortic lymph nodes. The occurrence of tumor growth beyond the inguinal lymph nodes leads to a poor prognosis for the patient and limits the therapeutical alternatives. Different ways of investigating the retroperitoneal lymph nodes are staging laparotomy, lymphography, lymphoscintigraphy, ultrasonography and computer tomography (zum Winkel 1972, Cohen et al 1975, Bernardino and Goldstein 1978). Staging laparotomy has been carried out on a small series of 26 patients with melanoma on the lower extremities (Cohen et al 1975). This was found to be of value for patients with clinically involved inguinal lymph nodes, but the small number of patients in this heterogenous series permits no definitive conclusions. Ultrasonography and computer tomography combined with the fine needle biopsy technique may be a more valuable alternative for staging melanoma patients. There are encouraging results from ultrasonography employed for this purpose and for evaluating therapeutical results in melanoma patients (Bernardino and Goldstein 1978). The advantage of ultrasonography is that it enables the assessment of many potential metastatic sites in the abdomen of the patient at one and the same examination. When objectively measurable tumors are found it is possible to repeat the examination and then obtain exact evaluation of the therapeutical effects. Estimation of the value of ultrasonography in advanced malignant melanoma has yet to be done.

An accepted method for the investigation of the lymphatic system is lymphography. However, this method is technically difficult and may be unpleasant for the patient (Koehler 1968, Kuisk 1971, Marglin and Castellino 1979). The traditional lymphographic technique involves the intralymphatic injection of radiocolloids both for diagnostic and therapeutic purposes (Ariel 1976, Steckel et al 1978, MRC Working Party 1979). An attractive alternative to this lymphography technique is lymphoscintigraphy with radiocolloids, using a scintillation camera technique (IV). The subcutaneous injection technique enables examination of lymph drainage of primary melanoma in any site of the body (fig 7) (IV).



Fig 7. Injection technique subcutaneously in the back of the foot with the patient under the scintillation camera to enable dynamic studies.

Other advantages of this technique are that the patient is not immobilized and that repeated examinations are possible. Dynamic studies of the lymphatic system by quantitative lymphoscintigraphy better reflect the functional status of the lymphatic system (IV). Disadvantages are that individual lymph vessels and lymph nodes are not visualized and that details of the lymph node anatomy cannot be seen. The images produced by the subcutaneous lymphoscintigraphic technique are well comparable with those produced by using the traditional lymphographic technique for injection of radiocolloids. Preliminary results indicate that results from the radionuclide perfusion examinations are comparable with the results of standard lymphography (Steckel et al 1978).

Several radiocolloids such as Gold-198-colloid or different Technetium-99-m-labelled colloids have been used for lymphoscintigraphy (Hultborn et al 1955, zum Winkel 1972, Ege 1977, Aspegren et al 1978). Initially promising results were obtained from the Gold-198-colloid, but the large absorbed dose caused local tissue necrosis and the high photon energy make this colloid unsuitable for scintillation camera measurements (zum Winkel 1972, Strand 1979). The absorbed dose to the injection site from Technetium-99-m-colloid is about 100 times less than that received from the Gold-198-colloid. The absorbed dose of Technetium-99-m-antimony sulphide colloid at the injection site varies from 40-170 mrad per mCi (10-45 μ Gy per MBq). The absorbed dose outside the injection site, however, will be extremely reduced due to the short range of the conversion electrons.

The qualities of Gold-198-colloid for visualizing the lymphatic drainage and the lymph nodes have been attributed to its ideal particle size (3-5 nm). In an experimental radiochemical study the qualities of different Technetium-99-m-labelled colloids have been investigated and related to the Gold-198-colloid (Strand and Persson 1979). From this study

it was obvious that there is a very narrow particle size range that permits radiocolloids to migrate into the lymph vessels while restricting passage to the blood. When the activity uptake in rabbit lymph nodes for different colloids used was studied, the Technetium-99-m-antimony sulphide colloid showed an activity uptake very close to that of Gold-198-colloid. This is the rational basis for using Technetium-99-m-antimony sulphide in clinical practice. When comparing Technetium-99-m-stannous phytate (< 5 nm) with Technetium-99-m-antimony sulphide colloid (5-15 nm) clinically by performing repeated examinations with the different colloids and comparing the lymphoscintigraphic imagings, the Technetium-99-m-antimony sulphide colloid was shown to be the most optimal (Kaplan et al 1979, Ege and Warbick 1979).

At lymphoscintigraphy, absence or defect activity uptake in the lymph nodes has been accepted as an indication of tumor infiltration (Göransson and Johnson 1974, Ege 1976, Aspegren et al 1978). For that purpose a high correlation between the activity uptake and the histopathology in the lymph nodes is of the greatest importance. In the present study, the activity uptake of Technetium-99-m-antimony sulphide colloid was 72 % in the benign lymph nodes and there was no uptake in the tumor infiltrated lymph nodes (IV). There is only one other study reported in the literature which has correlated the activity uptake in the lymph nodes with the histopathology and in that study only 50 % of benign lymph nodes show any uptake of the radiocolloid used (Technetium-99-m-sulphur colloid) (Aspegren et al 1978). The better activity uptake with the antimony sulphide colloid has to be related to the smaller particle size range (5-15 nm) compared with that of sulphur colloids (400-1 000 nm) (Persson and Naversten 1970). Further improved activity uptake can be expected if the injection sites are chosen so that the lymph drainage from the region investigated is covered.

Lymphography has been evaluated in two series of melanoma patients with conflicting results (Cox et al 1966, Musumeci et al 1976). Both these studies correlated the lymphographic findings with the histopathological findings. Cox et al (1966) reported a high number of false positive and false negative diagnoses, so that the method was considered to be of no value for the decision of patient management. In the other series of patients, the accuracy was good, but the evaluation was carried out separately for different parts of the removed lymph node chain from each patient (Musumeci et al 1976). Such an analysis can give no information about the probability that the patient with lymph node metastases has a pathological lymphography. The question about the value of lymphography in melanoma patients is therefore unsolved.

In patients with malignant melanoma of the trunk the lymph drainage can easily be visualized and can predict to which group of regional lymph nodes tumor cells migrate and cause metastases (IV) (Fee et al 1978, Meyer et al 1979). For this reason lymphoscintigraphy should now be included in the diagnostic arsenals for patients with trunk melanoma. The information obtained from lymphoscintigraphy is important, if lymph node dissection as a staging procedure is to be considered. During the clinical routine follow-up of these patients it is also important to know

which of the groups of regional lymph nodes is most likely to develop recurrent disease. An extension of quantitative lymphoscintigraphy, whereby the activity uptake is correlated to a more exact estimation of the tumor infiltration in the lymph node may increase the possibility of detecting lymph node metastases before enlarged lymph nodes occur. This should be of great value for staging patients with regard to retroperitoneal lymph node metastases.

Urinary melanogens in malignant melanoma

There has been extensive research regarding urinary metabolites in the melanine synthesis (urinary melanogens) which could be useful for diagnosing metastases from malignant melanoma and for estimating the tumor extent (Duchon 1977). The first reported test used on melanoma patients was the Thormählen-test which is mainly related to indole melanogens (Thormählen 1887, Duchon and Pechan 1963). This test is not applicable for clinical use because of its low sensitivity. Among the phenol melanogens, homovanillic acid (HVA) has found employment (Voorhess 1970, Morgan et al 1974, Trapeznikov et al 1975, Morgan et al 1976). Trapeznikov et al (1975) discovered a correlation between the clinical stage of patients with melanoma and the prognosis when the urine excretion of HVA was analysed.

Individual catechol compounds such as dopa, dopamine, cysteinyl-dopa have also been found to have increased urinary excretion in patients with disseminated malignant melanoma (Scott 1962, Voorhess 1970, Hinterberger et al 1972, Agrup et al 1975, Blois and Banda 1976). Different dopa compounds appeared elevated in about 8-44 % of examined patients but these compounds seem to lack value for the clinical judgment (Voorhess 1970, Hinterberger et al 1972). Blois and Banda (1976) reported on promising results when determining these compounds by an ion exchange column chromatography method. Their results indicated the possibility of detecting occult metastatic malignant melanoma and seemed useful for the diagnosis and follow-up of melanoma patients during therapy. Other investigators have shown that 5-S-cysteinyl-dopa may interfere with the determination of dopa, so it is plausible that the results of Blois and Banda (1976) are received by determining not only dopa but also 5-S-cysteinyl-dopa (Rorsman 1972).

5-S-cysteinyl-dopa is an aminoacid in the melanine synthesis and is the metabolite which is most constantly correlated to the occurrence of the melanoma metastases (I). 5-S-cysteinyl-dopa was first described in the melanoma patients with red hair (Björklund et al 1972), but since then it has been found in other melanoma patients regardless of their pigment (Agrup et al 1974). It has been demonstrated that 5-S-cysteinyl-dopa are products made and excreted by all active melanocytes (Rorsman et al 1979). 5-S-cysteinyl-dopa is not only a building stone of the red pigment (phaeo-melanins) but also of the dark pigment (eu-melanins) (Rorsman et al 1979). The urinary excretion is well correlated to the amount of melanine-producing cells in the body. Several methods for analysing 5-S-cysteinyl-dopa in the urine have been developed (Rorsman et al 1973, Burnett 1975, Banda et al 1977). A fluorimetric method has shown to be

FINE NEEDLE ASPIRATION CYTODIAGNOSIS OF RECURRENT MALIGNANT
MELANOMA.

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ABSTRACT

Sixty-four patients with melanoma (28 with clinical stage I disease and 36 with clinical stage II-IV disease) were fine needle biopsied on suspicion of recurrent melanoma. Eighty-four biopsies were aspirated percutaneously and three at exploratory laparotomy. A tumor mass was present at 81 biopsies. The remaining biopsies were taken with the guidance of liver scan or fluoroscopy. In the patients with the diagnosis of recurrent malignant melanoma the cytodiagnosis was correct in 45 patients out of 47. One patient was diagnosed as breast cancer and one as malignant mesenchymal tumor. Of 40 biopsies considered normal, three were revised to be melanoma. No false positive diagnosis was found. The frequency of false negative diagnosis was 6 %. Fine needle aspiration cytology is a suitable method to establish a correct diagnosis when there is a suspicion of recurrent disease during the follow-up of melanoma patients. The high diagnostic accuracy in patients with enlarged lymph nodes is excellent and makes the method preferable to diagnostic surgical excision biopsies.

INTRODUCTION

The outcome for patients with metastatic malignant melanoma has not been improved during recent years despite the application of various methods for treatment, i.e., surgery, chemotherapy, hyperthermia, and immunotherapy alone or combined (1). Surgery is still the basic and most important treatment for patients with metastatic malignant melanoma (2). Complementary chemotherapy is more suitable for patients with a small tumor burden, which signifies a better growth fraction and vascular supply, and thereby better drug response (3). An early diagnosis of recurrent melanoma is therefore important.

Usually melanoma patients are controlled regularly after treatment of the primary tumor. At these controls the patients are assessed by careful physical examination, laboratory tests, chest X-ray, brain scan, liver scan or bone scan depending on the clinical stage, and at which center the follow-up is performed.

At clinical signs of recurrent tumor, indicated either by the physical examination or by other diagnostic methods, it is important to confirm the correct diagnosis as soon as possible. Fine needle aspiration biopsy for cytodiagnosis of malignant disease has shown to be of great value. This technique has been used for several years in the diagnosis of breast cancer, different diseases of the lymph nodes, pulmonary tumors and intraabdominal tumors such as liver and pancreatic cancer (4, 5, 6). Cytodiagnosis has been used in melanoma patients mainly by direct smear from primary skin melanoma and from melanoma of the mucous membranes (7). Fine needle biopsies of metastatic malignant melanoma have been performed in a small number of patients (8).

The aspiration is easily performed when there is a palpable tumor mass, in addition as well as with the guidance of different diagnostic tools such as fluoroscopy, ultrasonography, angiography and computer tomography (6, 9, 10). The diagnostic accuracy of fine needle biopsy technique has been reported to be high (6).

The aim of the present study was to evaluate the fine needle aspiration biopsy technique used in melanoma patients when recurrent disease is indicated at the follow-up.

MATERIAL

In 64 patients (34 males and 30 females) 87 fine needle aspiration biopsies were taken due to suspected recurrent malignant melanoma. The patient series was followed at the section for surgical oncology, Department of Surgery, during

1971 - 1979. Of the 64 patients 28 were referred to clinical stage I and 36 to clinical stages II-IV according to Stehlin (11). Eighty-four of the 87 biopsies were aspirated percutaneously, and the remaining three during an exploratory laparotomy. The aspiration biopsy site in the patients is shown in Figure 1. A tumor mass was present at 81 biopsies. In the remaining patients the biopsies were taken with the guidance of liver scan or fluoroscopy. Sufficient material for diagnosis was obtained at aspiration on all occasions.

Fig 1. The aspiration biopsy site in 87 patients with suspected recurrent malignant melanoma.



The suspected tumor recurrence which was biopsied was found in 81 patients by physical examination at the follow-up. Fifteen per cent of the suspected recurrences were observed by the patients themselves. All the percutaneous fine needle aspiration biopsies were performed by an experienced cytologist.

TECHNIQUES

For the aspiration biopsy a 10 ml disposable plastic syringe fitted in an adaptor that permitted single-handed manipulation was used (CAMECO Ltd, Enebyberg, Sweden). A needle attached to the syringe had an outer diameter of 0.6-0.8 mm and a length varying from 25 to 80 mm. If there was a palpable mass the tumor was fixed with one hand and the aspiration performed with the instrument in the other hand. During maximum aspiration the needle was moved quickly back and forth in the lesion. The volume of the aspirated fluid was sufficient to fill the needle lumen and no more. The aspiration was discontinued before the needle was withdrawn from the lesion.

The aspirated fluid was transferred and smeared on one or two glass slides. The slide was then immediately fixed (before air-drying) in 95 % ethanol and stained with hematoxylin-eosin. Occasionally, the aspirated material was sufficient to allow for extra air-dried specimens stained with May-Grünwald-Giemsa.

A preliminary report was available as soon as 10-15 min after the aspiration had been performed.

RESULTS

The cytodiagnosis was malignant melanoma in 45 biopsies, malignant mesenchymal tumor in one and breast cancer in one. Fourty of the biopsies were classified as normal. In 37 of the 45 patients with the cytodiagnosis melanoma, the diagnosis was verified histo-pathologically. The macroscopical appearance of the tumors excised from the remaining eight patients was typical for that of malignant melanoma, i.e., heavy pigment-loaded lesions. The diagnosis of breast cancer and malignant mesenchymal tumor were revised to malignant melanoma after histo-pathological examination of the specimens. Both these tumors were amelanotic.

Of the 40 biopsies considered normal the diagnosis was revised in three. Two patients had typical liver metastases from malignant melanoma revealed at macroscopical examination at laparotomy. One patient had a wedge excision performed from a pancreatic lesion at the same time as the fine needle biopsy. The histo-pathological examination of the specimen showed typical melanoma tumor. No patients with regional metastases, i.e., satellitosis, in transit metastases, subcutaneous tumors or regional lymph nodes had any false negative cytodiagnosis.

No patients suffered any discomfort during the aspiration procedure and no complications were revealed afterwards.

The shortest follow-up time for patients with a normal cytodiagnosis is ten months and none of these patients have yet shown any clinical signs of recurrent melanoma. The diagnostic accuracy of the different tests was expressed according to the decision matrix shown in Table I (12).

DISCUSSION

Malignant melanoma metastasizes more widely than any other malignant tumor. The overall frequency of recurrent disease is approximately 60 % (13). Regional metastases, i.e., satellitosis, in transit metastases and regional lymph node metastases are seen in about 2/3 of patients with metastatic spread of malignant melanoma (14). The regional spread of

Table I. Decision matrix relating the results of diagnostic tests to pathological outcome. The number of patients in each group is put in parentheses.

	Positive cytodiagnosis	Negative cytodiagnosis	
Melanoma	a (47)	b (3)	a+b (50)
No melanoma	c (0)	d (37)	c+d (37)
	a+c (47)	b+d (40)	N (87)

a, b, c, d denotes the number of patients in each group. N = total number of patients.

$$\text{False negative tests} = 1 - \frac{a}{a+b}$$

$$\text{False positive tests} = 1 - \frac{d}{c+d}$$

$$\text{Predictive value of positive tests} = \frac{a}{a+c}$$

$$\text{Predictive value of negative tests} = \frac{d}{b+d}$$

the malignant melanoma is generally first observed by the physician at the clinical examination. This is especially applicable to subcutaneous recurrences and to lymph node metastases.

Initially there are no characteristic findings in the lymph nodes in patients with suspected recurrences. It is normally not possible to distinguish between early metastases to regional lymph nodes and benign enlargement of the nodes. An analogous diagnostic problem is found in patients with a primary malignant melanoma and palpable regional lymph nodes. Metastatic spread to regional lymph nodes directly influences the choice of further treatment, and the prognosis for the patients (1). The results in the present study have emphasized a high diagnostic accuracy of fine needle aspiration biopsies in enlarged lymph nodes. Thereby we can offer patients with a positive cytodiagnosis of melanoma immediate surgical treatment without any delay caused by excised biopsies.

Screening procedures used for melanoma patients, such as chest X-ray and liver scan, are associated with both false positive and false negative results (15). Of these methods, chest X-ray is unquestioned and the most regularly used (16). It is well-documented that patients may have a shadow on chest X-ray at the same time as the diagnosis of the primary malignant melanoma (17, 18). This lung shadow does not have to be a metastasis of the melanoma, but in many cases might be a benign tumor or a primary lung cancer (18). Percutaneous fine needle biopsy of the lung tumor in these patients will give a correct diagnosis immediately.

It is postulated that fine needle aspiration biopsy should be used with restriction in melanoma patients, as seeding of tumor cells along the needle tract may occur more frequently in malignant melanoma than in other malignant tumors.

Percutaneous biopsy of the liver and of the thyroid was in the present series done in eight patients. None of these patients developed metastases along the needle tract. In the patient with a pancreatic metastasis a wedge excision was performed at laparotomy and after that the lesion was drained percutaneously. Within 30 days a massive tumor growth in the drain channel was seen. Local recurrences were seen in 6 patients after extensive regional lymph node dissection performed in 21 patients with metastatic melanoma of the lymph nodes. Local recurrences after lymph node dissection may be related either to seeding of tumor cells in the needle tract after the biopsy or to tumor spread at the lymph node dissection or to remaining tumor after the surgery. It is impossible to prove which of these three that is the causal mechanism for recurrence.

A biopsy verified diagnosis of metastatic malignant melanoma is mandatory before any treatment with cytostatic agents is commenced. It is also of great importance to have the correct diagnosis early as it is then possible to offer in some patients further surgical treatment. In this respect fine needle biopsy is very suitable.

The diagnostic accuracy of the performed biopsies in this series was very high (Table I). The predictive value of a positive test, which denotes the probability of a patient with such a test to have the disease was 100 %. The predictive value of a negative test was 93 %. The high predictive values are correlated to the great prevalence (54 %) of melanoma metastases in the series. There have not been any false positive diagnoses and the frequency of false negative diagnoses was only 6 %.

All the cytodiagnoses of secondary malignant melanoma were verified histopathologically. Among the normal examination

results there were three false negative ones. In one of these, the diagnosis of malignant melanoma could be verified by knife biopsy and histopathological examination. In two patients the findings of a macroscopically tumor involved liver and the clinical course afterwards convinced us that the cytodiagnosis was wrong. In all patients with local or regional recurrences the established cytodiagnosis was correct.

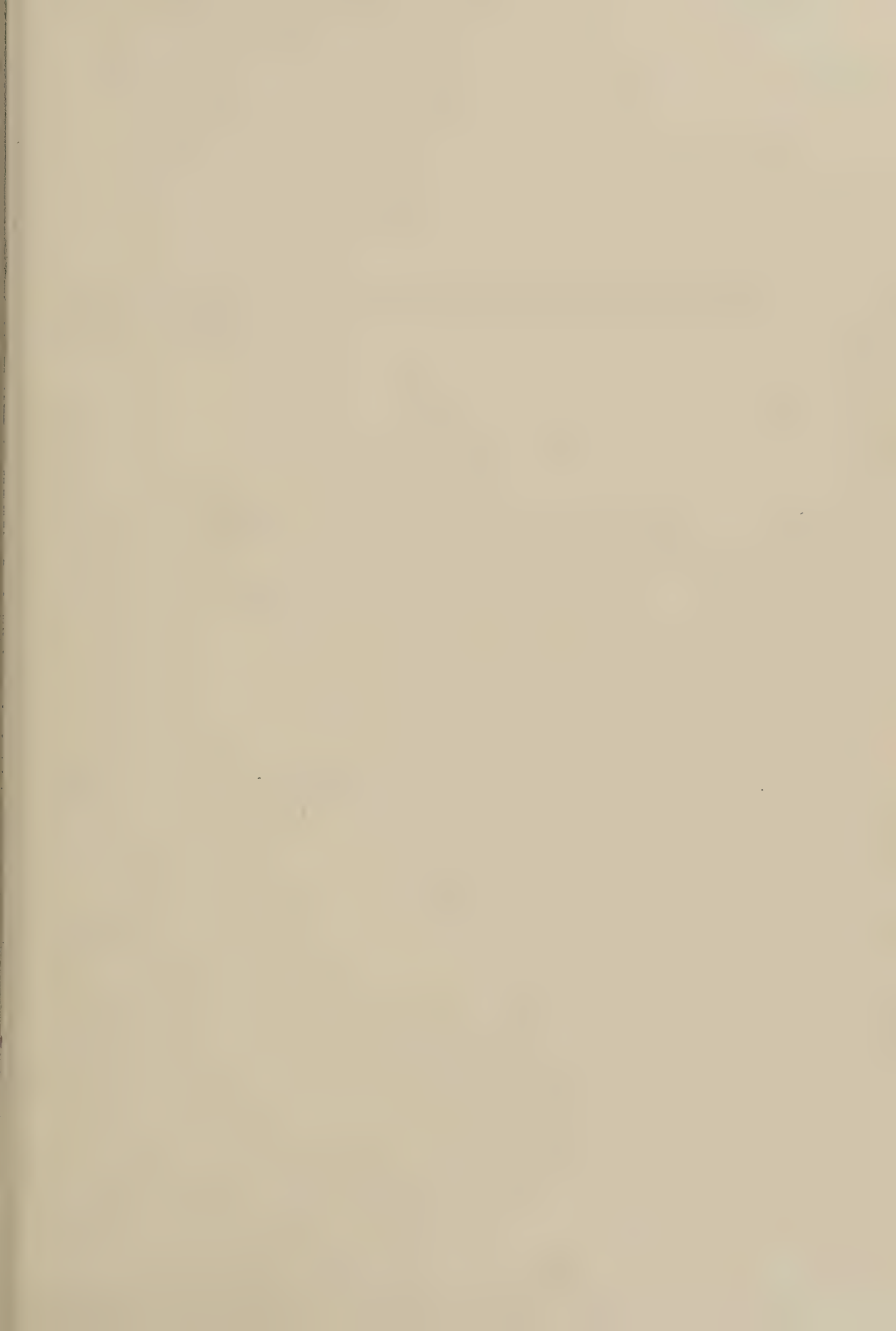
In malignant melanoma it must be stressed that the examination is performed by an experienced cytologist and that the correct diagnosis is established in connection with the aspiration procedure. If there is no representative material in the aspiration it is advisable to re-aspirate the patient immediately. As that tumor cell contamination in the needle tract constitutes an extra risk factor, it is important to operate the patients with a positive cytodiagnosis as soon as possible after the biopsy.

Fine needle aspiration biopsy is suitable for combination with non-invasive diagnostic methods such as ultrasonography and computer tomography. The method gives us the possibility of a correct diagnosis not only of suspected recurrences on the body surface, but also of deep intraabdominal recurrences, i.e., in the liver or retroperitoneal area, where metastatic spread of malignant melanoma so far has been very difficult to diagnose. The high diagnostic accuracy in patients without melanoma in enlarged lymph nodes is excellent and makes the method preferable to diagnostic surgical excision biopsies. Other advantages of the method are that it minimizes the discomfort of the patient and can be performed on an out-patient basis.

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HYPERTHERMIC PERFUSION OF RECURRENT MALIGNANT MELANOMA
ON THE EXTREMITIES.

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ABSTRACT

Twenty-one patients with recurrent malignant melanoma on the extremities were treated by regional hyperthermic perfusion with melphalan (Alkeran^R). Four patients had a second perfusion. The recurrence site was on the foot in one patient, on the lower part of the leg in 13 patients, below the mid thigh in six patients and on the elbow in one patient. The temperature of the extremities was registered continuously during the perfusion. The perfusion was performed under hyperthermic conditions with a temperature of 40-41.0°C i.m.. The perfusion time was two hours. Alkeran was given in a dose of 0.9 mg/kg bodyweight for lower extremity perfusion and 0.45 mg/kg for upper extremity perfusion. Complete tumor regression or more than 50 % tumor regression was registered in eight out of the ten patients with manifest tumors. As the first sign of recurrence after perfusion four patients had local recurrence and ten patients systemic recurrence. Altogether one third of the patients had local recurrences and half of the patients systemic recurrences. Local recurrences occurred after a median time of eight months and systemic recurrences after a median time of seven months. Ten patients are still alive after an observation time of 5.5 months to 44 months. Six patients are without any signs of recurrent disease.

INTRODUCTION

The unpredictable course of malignant melanoma is a challenge to the different therapeutic procedures available. Although various methods of treatment have been employed, such as surgery, cytostatic therapy and immunotherapy, alone or combined, the outcome for patients with metastatic malignant melanoma remains poor (1). To achieve a better response to cytostatic therapy attempts have been made with various methods of administering the drugs. In 1958 Creech et al (2) presented a regional isolated perfusion technique developed from the regional infusion technique described by Klopp in 1950 (3). There were then no new innovations in this field until Cavaliere et al (4) in 1966 described their experience of regional hyperthermic perfusion. Based on this Stehlin developed the regional hyperthermic perfusion technique with cytostatic drugs (5, 6).

In an isolated perfusion system the tumor-bearing region is subjected to the influence of a high concentration of a cytostatic drug in such a way that it does not contaminate other parts of the body to any important extent (2, 5). Malignant melanoma of the extremities seems especially suited for this treatment, because regional metastases, i.e., satellitosis, in transit metastases and regional lymph node metastases occur in up to 20 % of patients with recurrent melanoma (7).

The aim of the present study was to evaluate the technique for regional controlled hyperthermic perfusion with cytostatic drugs in patients with regional metastases from malignant melanoma on the extremities.

MATERIAL AND METHODS

In 1976-1979, 21 patients (7 men, 14 women, age range 46-78 years, median age 64 years) with recurrent malignant melanoma on the extremities were treated by regional hyperthermic perfusion with melphalan (Alkeran^R). The diagnosis was verified histopathologically or cytologically in all 21 patients. Four of these patients were given a second perfusion five to 19 months after the first. The indications for perfusion treatment were local recurrences or regional metastases (in transit metastases) distal to the upper third of the upper and lower extremities with or without regional lymph node metastases. The patients were staged according to the classification reported by Stehlin and others (6, 8) (Table I). In this study, the clinical stages were based on the pre-treatment evaluation and revised according to the results of regional lymph node dissection.

The site of recurrences treated by perfusion was on the foot

Table I. Staging of 21 patients according to Stehlins' classification.

Stage	Patients n	Definition of stage (Stehlin)
II	7	Local recurrence; within or adjacent to the scar of the primary lesion.
III A	3	Regional metastases; in transit disease or satellitosis; nodes negative clinically or microscopically.
III B	6	Regional metastases; nodes positive clinically or microscopically.
III AB	4	Regional metastases; combined in transit disease and metastases to regional nodes.
IV	1	Distant metastases; includes metastases to supraclavicular nodes, and to iliac or obturator nodes.

in one patient, on the lower part of the leg in 13 and below mid thigh in six patients. One patient had the recurrence on the elbow which was treated with an upper extremity perfusion.

The pretreatment evaluation for all the patients included a physical examination, laboratory tests (Hb, WBC, platelet count, S-Bil, S-ALP, S-ALAT, S-ASAT and urinary excretion of 5-S-cysteinyldopa) and chest X-ray. Liver scan was performed in 19 patients, brain scan or computer tomography of the brain in 13 patients.

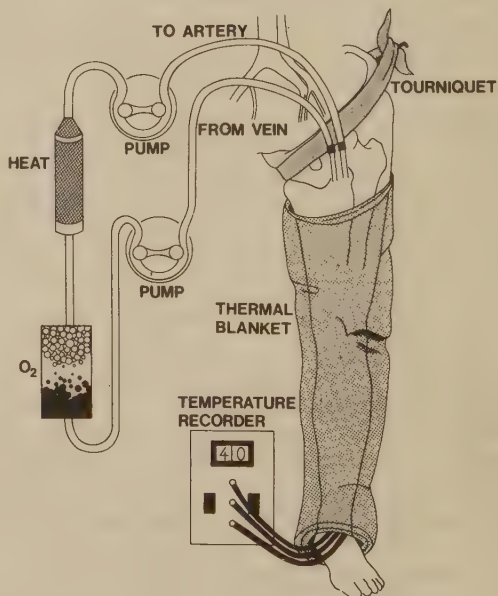
Four times annually after the operation regular check-ups were carried out with clinical controls, laboratory tests, chest X-rays and liver scans. Brain scans or computer tomography were performed when any signs of neurological symptoms appeared. The follow-up ended on December 31, 1979. The shortest follow-up time was eight months.

The objective tumor response in ten patients with manifest tumor during the perfusion treatment was evaluated by regular clinical examinations and by histopathological examinations after delayed excision.

The regional hyperthermic perfusion technique

Thermocouples for continuous monitoring of the temperature were placed intramuscularly, subcutaneously and cutaneously at different levels of the extremity and in the rectum, and connected to an ELLAB digital temperature recorder. To avoid heat loss, the extremity was isolated with a mattress containing circulating water at 38°C and a plastic sheet. The femoral artery and vein were used for the perfusion. After systemic heparinization, the vessels were isolated and cannulated (steel cannula $\varnothing$ 4-5 mm) and connected to an extra-corporal perfusion circuit (Fig 1). A rubber Esmarch tourniquet was tied around the extremity proximally to the entrance into the vessels and fixed over a rush pin percutaneously inserted in the iliac crest. The perfusion circuit consisted of a pediatric heart-lung machine with a membrane oxygenator and heat exchanger. The perfusion fluid consisted of blood and Ringer solution and its temperature was maintained at approximately 41.5-42°C by the heat exchanger. The perfusate pressure was kept below the mean systemic arterial blood pressure. The pO_2 , pCO_2 and pH of the patients' blood and perfusion were measured repeatedly. The flow rate was 400-600 ml/min.

Fig 1. Schematic view of technique for regional perfusion of lower extremity with cytostatics and controlled hyperthermia. The extremity is isolated with a heating mattress. Thermistor probes are inserted for continuous registration of the temperature in the extremity.



The cytostatic agent used was melphalan (Alkeran^R) in a dose of 0.9 mg/kg bodyweight. Half the amount of Alkeran was given to the patient when the intramuscular temperature had risen to 37-38°C, the other half of the dose one hour later. The perfusion time was two hours.

At the end of the perfusion the extremity was rinsed with 1.7 l Ringer solution. The cannulae were withdrawn and the vessels repaired. The anti-coagulant effect of heparin was neutralized with equivalent doses of protamine sulphate.

The perfusion of the upper extremity was performed in basically the same way using the axillary artery and vein and a lower dose of melphalan (0.45 mg/kg bodyweight). In this case the flow was 200-300 ml/min.

Surgical treatment of regional lymph nodes

A staging inguinal lymph node dissection was performed before isolating the vessels. For the same purpose, the lymphatic tissue around the common iliac vessels was also dissected through a separate incision five cm above and parallel with the inguinal ligament. Suction drains were placed in the subinguinal area and the wound was closed after resection of the skin edges to avoid necrosis. A staging axillary node dissection was performed for the upper extremity perfusion.

Postoperative care

On the first postoperative day the patients were mobilized and active exercises of the perfused limb was started to prevent thrombosis. The extremity was wrapped with an elastic bandage. Dextran 40 (Rheomacrodex^R) was given in five days to improve blood flow and prevent thrombosis. Antibiotic prophylaxis with Cephalosporin (Keflin^R) was started at operation and continued for ten days. To prevent oedema in the extremity, the diuretic furosemid (Lasix^R) was given regularly.

Further treatments

The recurrent lesions were excised before the perfusion in 11 patients. In eight patients a delayed radical excision four to six weeks after the perfusion was performed. Two patients with wide spread of in transit metastases of the extremity had only occasional lesions excised surgically.

Systemic chemotherapy (DTIC-DOME^R) was administered to six patients when they developed distant metastases. Two patients with liver metastases were treated by temporary liver dearterialization followed by regional DTIC infusion in the hepatic artery.

RESULTS

Hyperthermia

The temperature of the extremity rose from 32-33°C at commencement of procedure to the level of 40-41°C during perfusion. When the perfusion circuit was open the temperature was 35°C and after 20 min it rose to 38°C after which the cytostatic agent was administered.

Tumor response

All patients with manifest tumor at time for perfusion treatment had a tumor response registered judged by clinical examination (Table II). In one patient this effect could not be verified by the histopathological examination. The patient with total tumor regression had a cytologically verified tumor localized on the elbow with two perpendicular diameters of 2 and 3 cm. This tumor had shrunk to a diameter less than one cm and the histopathological examination of the excised specimen four weeks after perfusion showed no viable tumor cells.

Table II. The evaluation of treatment effect on manifest tumor.

Percentage regression of local tumor	Patients n = 10
100	1
> 50	7
< 50	1
0	1

Recurrent disease

The relation between the site of the perfused recurrence and the clinical stage related to further recurrences after the treatment is shown in Table III. Four patients had a local recurrence on the perfused limb as the first manifestation of tumor progress after the perfusion treatment. In three of these patients it was the only manifestation of the disease. Further three patients with local recurrences had distant metastases at the same time.

Ten patients had systemic metastatic spread of the disease as the first sign of recurrence. One of these developed regional metastases later on. Altogether one third (33%) of the

patients had local recurrences after the perfusion treatment. The median time after perfusion for a new local recurrence was eight months (range 1-20 months) and for systemic recurrence seven months (range 4-29 months). Of the four patients who were reperfused three are still alive, two in a stationary good condition and one with a surgically excised local recurrence 20 months after the second perfusion. One patient succumbed from brain metastases three months after the reperfusion.

	Upper part of of the limb	Lower part of the limb	Foot
The localization of the treated recurrence	6 (1)	13	1
Positive regional lymph nodes	5 (0)	6	0
Localization of the first recurrences after the perfusion			
Local	0	7	0
Distant	5 (1)	2	0

Table III. The results of perfusion treatment with reference to regional lymph node dissection and recurrence site. All are related to the site on the extremity of the tumor which was treated. Figures in parenthesis indicate the upper extremity perfusion.

Survival

One patient died one month after the perfusion. Postmortem examination showed a cerebral haemorrhage but there were no signs of malignant melanoma. A further ten patients died 6.5-36 months after the perfusion (median time 17 months). In these patients systemic metastases were verified after a median time of seven months (range 4-29 months).

There was one patient who developed recurrent disease subcutaneously on the trunk after 12 months and in the retroperitoneal lymph nodes after 20 months. This patient was treated successfully with systemic chemotherapy and is still alive 43 months after the perfusion treatment. Four patients with manifest regional tumor recurrences are alive 11, 16, 43 and 44 months respectively after the perfusion treatment. One patient, reperfused after 20 months, is still alive after 44 months. Six patients without any signs of recurrent tumor are alive after 5.5, 6.5, 16, 21, 28 and 43 months respectively.

Complications

There were no toxic effects on the bone marrow registered in any patient. A third degree burn was caused by a heat lamp which unfortunately irradiated the skin of the upper part of the limb of one patient. The injury was excised and covered with split skin grafts and healed uneventfully. Wound infection was seen in four patients, hematoma in five and seroma in eight.

DISCUSSION

Since the report from Creech there have been about 20 publications on the results of regional perfusion. More than half of these have been presented after 1975 (6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20). Only five of these reports are on controlled hyperthermic perfusion (6, 16, 17, 19, 20). The rest concern perfusion with perfusate at body temperature. In many patients with manifest tumors complete tumor regression or more than 50 % tumor regression has been reported (36-100 %) (6, 9, 15, 16, 18, 19). In the present series such a tumor response was registered in eight out of ten patients (80 %).

The survival times in the different series of patients with recurrences or metastases clinically confined to the extremity cannot be compared because of the lack of uniformity in classification and in performance of the perfusion treatment. Other important factors to be kept in mind when evaluating different series of perfusion treatment are the temperature level, perfusion time, cytostatic agents, oxygenations etc. In a study of 73 patients with local recurrences and in transit metastases (stage II, IIIA, IIIB, IIIAB) subjected to hyperthermic perfusion there was a five year survival rate of 52.5 % (21). In a comprehensive review of 30 patients (stage IIIA) treated with hyperthermic perfusion and 27 patients (stage IIIA) treated with surgical excision with or without normothermic perfusion the five year survival was 76.7 % compared with 22.2 % (6).

There are two other series of regional normothermic perfusion showing 28 % and 39 % five year survival (22, 11). Other series (9, 15, 17, 23) reveal two and three year survival from 30-65 %. Even if all these series are not comparable they indicate a somewhat lower survival than Stehlin had in his hyperthermic series and are more in line with the series treated by surgical excision or amputation. The five year survival after major amputation varies between 15-33 % which is somewhat better than the five year survival of 20 % for patients treated by surgical excision (24, 25, 26).

Nearly all patients with regional lymph node metastases will get distant metastases after perfusion (22). This is in agreement with the difference in five year survival between patients with extensive regional metastases and patients with solitary cutaneous or subcutaneous metastases on the extremity which is from 17-67 % (22). In the present series five out of six patients had systemic metastases after regional hyperthermic perfusion when the melanoma was localized to the thigh (Table III). It is therefore some doubt about the suitability of hyperthermic perfusion for recurrent melanoma on this site. Whether surgical excision, or surgical excision combined with regional hyperthermic perfusion is to be preferred for recurrences on the lower part of the extremity is not established in the present series. This question may be answered in a prospective randomized stratified clinical trial.

Various methods for the estimation of the leakage from the perfusion system have been worked out (10, 27). The leakage from iliac and femoral perfusion is almost the same. After one hour of perfusion the leakage was shown to be 10-30 % (27) and presumably this is higher when the perfusion time is two hours. After leakage of 62 %, severe bone marrow depression was established (28). To prevent leakage from the extremity, the perfusion pressure was maintained below the mean systemic arterial pressure. In the present series, the blood count revealed no effect on the bone marrow indicating a leakage of less magnitude. Myelosuppressive effects related to the leakage of the drug seem to be limited, being reported in 4 % in a review of 2 000 perfused patients (29).

After instituting hyperthermic perfusion an increased number of complications such as oedema, local burns, nerve injuries and renal failures have been observed (5, 30). The nerve injuries may be a toxic effect of the combination of the drug and the heat or an acute compartment syndrome (31). This acute syndrome may be due to mechanical disturbances in the local circulation caused by damage to the permeability of blood vessels from hypoxia, heat and chemotherapy. In 13 cases out of approximately 2 000 perfusions, an amputation of the perfused leg had to be performed mainly due to tissue necrosis (29). The overall complication rate in the present study and in others is not of such magnitude that the procedure is contraindicated in more than exceptional cases (22, 6).

Controlled hyperthermia means intramuscular perfusion performed at a temperature above 40°C during the perfusion time. When combining perfusion with melphalan and heat the synergistic effect between increased temperature and alkylating agents is exploited. Experimental studies in rats

with transplanted melanoma have formed the basis for the use of melphalan (32). The theory was that phenylalanine would carry cytostatic radicals into the melanine metabolism of the melanoma cells. For this reason melphalan was tried in isolation perfusion for melanoma and is still the main drug used.

In conclusion, hyperthermic perfusion has an oncolytic effect on malignant melanoma and may give some patients local control of the disease with a prolonged survival time. There are, however, many unanswered questions, e.g., the theoretical background for the effect of the perfusion technique, the optimal temperature, the optimal duration of the perfusion oxygenation etc. There has to be done far more research in this field regarding the technique of the perfusion. Certainly controlled randomized studies of melanoma and other tumors will be most welcome.

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QUANTITATIVE LYMPHOSCINTIGRAPHY II: IMAGING TECHNIQUE,
DOSIMETRY AND HISTOPATHOLOGY IN PATIENTS WITH MALIGNANT
MELANOMA.

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KEY WORDS

Scintillation camera, quantitative measurement, malignant melanoma, Tc-99m-antimony sulphide colloid, lymph nodes, lymphoscintigraphy.

ABSTRACT

A quantitative scintillation camera technique has been developed for investigation of the lymph drainage and the uptake of $^{99}\text{Tc}^{\text{m}}\text{Sb}_2\text{S}_3$ -colloid injected subcutaneously in patients with malignant melanoma. A model was designed for calculating absorbed doses to the injection site, the lymph nodes and the whole body based on these findings. The scintigraphic findings were correlated with histopathology of the surgically removed lymph nodes. Five patients with melanoma of the trunk and four patients with melanoma of the lower extremities were examined. Sequential images were taken every 15 sec the first two hours after the injection in patients with melanoma on the lower extremities. After four to six hours static images were taken of all patients. On the following day lymph node dissection was performed and the specimen was measured for radioactivity and examined by light microscopy. Lymph drainage from the injection site to regional lymph nodes was shown in all nine patients. In three patients a reduced activity uptake was found, which was correlated to histopathological findings of metastases in one patient. A total of 74 lymph nodes were individually examined. Five lymph nodes were infiltrated with malignant melanoma. No activity uptake was seen in the malignant lymph nodes whereas 50 of the benign lymph nodes had an activity uptake. The absorbed dose to injection site varied from 10-45 mGy per MBq. The activity content rarely exceeds 0.1 % of the injected activity in individual lymph nodes. With a weight of 0.8 g and an activity uptake of 0.1 % in a lymph node the absorbed dose would be about 0.1 mGy per MBq of injected activity.

INTRODUCTION

There is an urgent need of a method for examining the lymphatic drainage and lymph nodes for metastases. Although lymphography is an accepted method for investigation of the lymphatic system (1), it is not always applicable because the contrast has to be injected into a suitable lymph vessel, moreover some clinical contraindications limit its use (2, 3).

An attractive alternative is lymphoscintigraphy, which is safe and simple and has technical advantages (4, 5, 6). Several lymphoscintigraphic studies have been made both in animals and in humans using ^{198}Au colloid or different $^{99}\text{Tc}^{\text{m}}$ labelled colloids (5, 6, 7). The disadvantage of using ^{198}Au colloid despite its favourable particle size is the high photon energy for scintillation camera measurements and its high absorbed dose which may cause local tissue necrosis (4).

In a recent experimental radiochemical study it was shown that $^{99}\text{Tc}^{\text{m}}$ -antimony sulphide colloid has a particle size comparable with that of ^{198}Au colloid (8). In the studies of the activity uptake in parasternal lymph nodes of rabbits it was found that $^{99}\text{Tc}^{\text{m}}$ -antimony sulphide colloid had an activity uptake of 5 % of the injected activity compared with 8 % for the ^{198}Au colloid (8).

In order to apply these findings to clinical practice the following investigation was initiated. Firstly a quantitative scintillation camera technique was developed for the investigation of the lymph drainage and the uptake of the $^{99}\text{Tc}^{\text{m}}$ -antimony sulphide colloid in lymph nodes of patients with malignant melanoma and secondly a model was designed for calculating the absorbed doses to the injection site, the lymph nodes and the whole body on these observations. Finally the scintigraphic findings in the patient studies were correlated to histopathology of the surgically removed lymph nodes.

MATERIAL AND METHODS

Radiopharmaceuticals

In a previous experimental study it has been shown in rabbits that the most suitable radiocolloid for lymphoscintigraphy is the $^{99}\text{Tc}^{\text{m}}$ -antimony sulphide colloid (Labelaid DRN 4333 Philips Duphar, B. V. Petten, Holland) $^{99}\text{Tc}^{\text{m}}\text{Sb}_2\text{S}_3$ (8). The range of the particle size for this colloid is 5-15 nm (5, 8, 9, 10, 11) and is consequently small enough to pass from the interstitial fluid through the lymphatic capillary pores to the lymphatic vessels. The precolloid kit was mixed with

about 20 mCi of pertechnetate ($^{99}\text{Tc}^{\text{m}}$ -generator, nominal activity 500 mCi, New England Nuclear) in 7 ml saline. After cooling, 0.5 ml of the colloid with about 1.0 mCi (37 MBq) was drawn into a syringe and injected subcutaneously.

Before using the preparation, its radiochemical characteristics were checked with gel chromatography column scanning (8, 11, 12). In all the preparations less than 3 % of the activity was due to free pertechnetate and 90 % of the activity was labelled to particles in the desired size interval 5-15 nm.

Clinical Investigations

Nine patients with malignant melanoma were examined (Table I). The colloid was injected subcutaneously. In five patients with melanoma of the trunk, the colloid was injected around the site of the excision of the primary lesion, and in four patients with melanoma of the lower extremities the injection site was on the back of the foot (Fig 1). As a control, an identical injection procedure was carried out at the same time on the contralateral side of the body, in all but two patients with melanoma of the trunk whose control side was examined four weeks after the initial procedure.

Patient No	Age/Sex	Primary tumor site	Direction of lymph flow
1	57/m	5 cm cranial to the umbilicus	Right and left ingue
2	26/m	Left flank over thorax	Left axilla
3	79/m	Left shoulder	Left axilla
4	62/f	Left lower leg	Left ingue
5	66/m	Mid sternum	Right and left axilla
6	56/f	Right lower leg	Right ingue
7	66/f	Left lower leg	Left ingue
8	54/m	Right shoulder	Right axilla
9	43/f	Right lower leg	Right ingue

Table I. Lymph flow related to the primary tumor site.

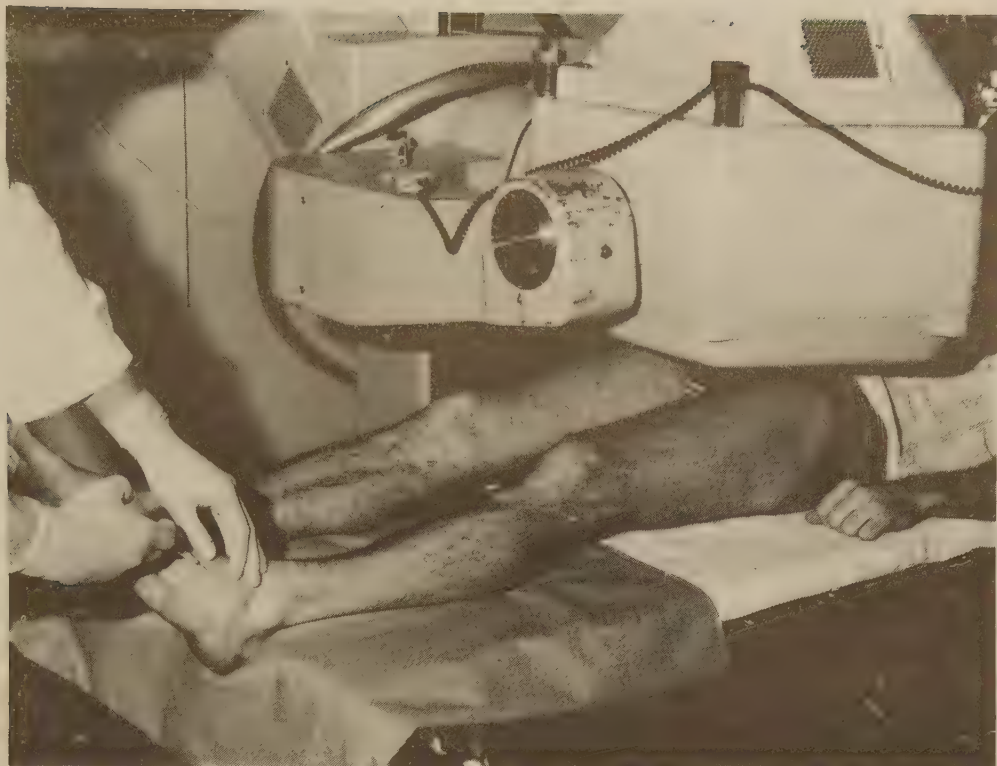


Fig. 1. Injection technique subcutaneously in the back of the foot with the patient under the scintillation camera to enable dynamic studies.

Sequential images over the iliacal, inguinal and lower lumbar lymph nodes of the patients with melanoma of the lower extremities were taken with a scintillation camera every 15 sec in order to examine the dynamics of the lymphatic drainage. These studies were performed during one to two hours after the injection. Static images were taken of all the patients 4-6 hours after the injection to identify activity uptake in the lymph nodes.

Quantitative Measurements

The quantitative activity uptake in the areas of lymph nodes seen in the camera image was calculated from the net number of counts $N(t)$ in a region of interest with the background activity subtracted. Using the known calibration factor $\alpha(d)$ for the scintillation camera, i.e., the count rate per unit of activity for the actual depth d of the lymph nodes (6) and the injected activity $A(0)$, the percentage uptake $P(t)$ in each lymph node area can be calculated according to

$$P(t) = \frac{N(t)}{\alpha(d) \cdot A(0)} \cdot e^{-\lambda t}$$

The depth d of the lymph nodes was estimated either from anterior-posterior measurements or from lateral views (6, 13).

In Vitro Measurements

On the day after the scintillation camera imagings, the patients were operated. For cases of trunk melanoma, unilateral axillary lymph node dissection was made in four patients and bilateral axillary node dissection in one. Iliio-inguinal lymph node dissections were carried out on all patients with melanoma of the lower extremities. In the specimen from five patients each lymph node was isolated, weighed and put into separate plastic test tubes with formalin. The activity of the lymph nodes was measured with an automatic sample changer NaI(Tl) well counter.

The activity uptake in a lymph node was calculated by comparing the count rate from the node with a standard, prepared from the $^{99}\text{Tc}^{\text{m}}$ colloid vial used for the injection.

Each lymph node was fixed in 10 % formaldehyde, embedded in paraffin, sectioned at 5 μm thickness and routinely processed and stained with hematoxylin-erythrosine and in some cases with Masson's melanin pigment stain. The slides were examined by light microscopy.

Dosimetry

The absorbed doses to the injection sites and the individual lymph nodes were calculated according to the recommendation of the MIRD Committee (14) and/or using a computer program for internal dosimetry developed by some of us for calculations of absorbed fractions (15). The actual measured uptake values and weights for the lymph nodes were used.

In order to estimate the absorbed dose to the gonads two theoretical cases have been considered where the injection site is 10 cm and 20 cm from either the ovaries or testes. Using the formula

$$D_{\text{tot}}(r) = \int_0^{\infty} \dot{D}(r) dt = \int_0^{\infty} \dot{\phi} \cdot h\nu \frac{1}{4\pi \cdot r^2} \cdot \left(\frac{\mu_{\text{en}}}{\rho}\right)_{\text{h}\nu} \cdot B_{\text{en}}(\mu r) \cdot \exp\left\{-\left(\frac{\mu}{\rho}\right) \cdot (\rho r)\right\} \cdot dt$$

where ϕ is the photon fluence rate equal to the injected activity $A(0)$ times the number of emitted photons per dis-

integration, $h\nu$ the photon energy (140 keV), r the distance between the injection site and the target organ, μ_{en}/ρ the mass energy absorption coefficient (equal to $0.0273 \text{ cm}^2\text{g}^{-1}$), $B_{en}(\mu r)$ the energy absorption buildup factor (equal to 6.5 for $\mu r = 1.53$ mean free paths and 18.3 for $\mu r = 3.06$) and μ/ρ the linear mass attenuation coefficient (equal to $0.153 \text{ cm}^2\text{g}^{-1}$).

With these values the absorbed dose to the gonads will be, with the distance r equal to 10 cm

$$D_{\text{tot}} = 70 \text{ mrad per mCi } ^{99}\text{Tc}^{\text{m}} (= 19 \text{ }\mu\text{Gy per MBq})$$

If the distance r is increased to 20 cm, then

$$D_{\text{tot}} = 10 \text{ mrad per mCi } ^{99}\text{Tc}^{\text{m}} (= 2.7 \text{ }\mu\text{Gy per MBq})$$

Corresponding values from the computer calculations gave 80 and 15 mrad per mCi $^{99}\text{Tc}^{\text{m}}$ (or 21.6 and 4.1 $\mu\text{Gy per MBq}$) respectively.

In order to calculate the absorbed dose to the whole body using the S formalism given by the MIRD Committee (16) and utilizing a geometry given by MIRD for the calculations, it was assumed that the activity was equally distributed in the stomach. The absorbed dose per cumulated unit activity S is then $1.9 \cdot 10^{-6} \text{ rad} \cdot \mu\text{Ci}^{-1} \cdot \text{h}^{-1}$ and the absorbed dose will thus be 16 mrad per mCi $^{99}\text{Tc}^{\text{m}}$ (4.3 $\mu\text{Gy per MBq}$).

The computer program calculations of the absorbed dose to the whole body were based on an assumption that the activity was injected either into the back of the foot, or the abdominal wall in the vicinity of the umbilicus. In the former case, an absorbed dose of 0.7 mrad per mCi $^{99}\text{Tc}^{\text{m}}$ (0.2 $\mu\text{Gy per MBq}$) and in the second case of 9 mrad per mCi $^{99}\text{Tc}^{\text{m}}$ (2.2 $\mu\text{Gy per MBq}$) was calculated.

The activity in a total of 13 injection sites in seven patients has been measured in order to calculate the absorbed dose to the injection site. After about five hours there still remained 78-99 % of the injected activity with a mean activity of $(90 \pm 7) \%$ ($\pm \text{S.D.}$).

It was assumed that the flow rate k of the colloid from the injection site could be approximated with a monoexponential outflow. With 80 % remaining activity after five hours, the rate constant will be 0.045 h^{-1} .

If the decay constant λ for $^{99}\text{Tc}^{\text{m}}$ is 0.115 h^{-1} , then the cumulated activity $\tilde{A}$ is expressed

$$\tilde{A} = \frac{A(0)}{k + \lambda}$$

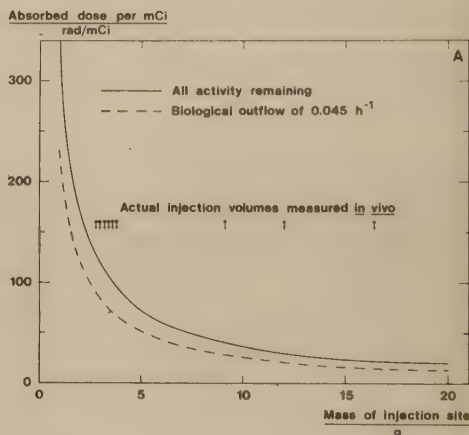
or $6.2 \cdot A(0)$ with 80 % and $8.7 \cdot A(0)$ with 100 % remaining at the injection site.

From these data the absorbed dose to the injection site can be calculated using the MIRD formalism

$$D_{\text{tot}} = \tilde{A}(0) \cdot \Delta_1 \cdot \phi(v+r) \cdot \frac{1}{m}$$

The area of the injection site was estimated from actual measurements on the scintillation camera images and the volume was calculated to lie between 3 and 20 cm³. If it is assumed that the activity is uniformly mixed in the interstitial fluid, then the absorbed dose can be calculated for masses of the injection site between 1 and 20 grams. The results are given in Fig 2 A.

Fig. 2 A. The absorbed dose to the injection site for different volumes on the injection sites. Curves are given for the injected activity of 1 mCi for 2 extremes, when all the activities remain in the injection site and when only 80 % of the activity remains after 8 hours.

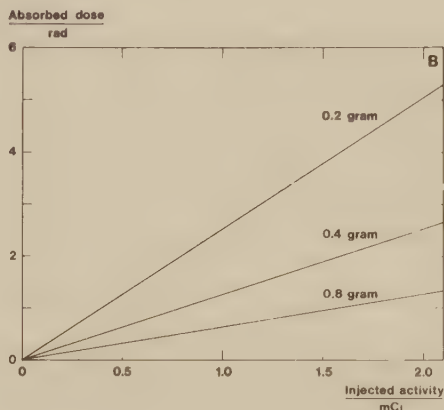


The in vitro measurements of the individual lymph nodes show that the activity uptake was less than 1 % of the injected activity. Denoting k_2 as the rate constant for the flow of activity from the injection site to one lymph node and k_1 as the flow of activity to other sites, the following calculations could be done. In order to estimate the absorbed doses to a single lymph node, the average case in this investigation can be considered to have 90 % of the remaining injected activity in the injection site after five hours. This gives a rate constant $k = k_1 + k_2$ from the injection site of 0.021 h^{-1} and a rate constant k_2 for 0.1 % uptake in a lymph node of 0.00021 h^{-1} . The cumulated activity in a lymph node $\tilde{A}_{lg1}$ is then expressed

$$A_{lg1} = A(0) \cdot \frac{k_1}{\lambda(k_1 + k_2 + \lambda)}$$

which gives $\tilde{A}_{lg1} = 0.0134 \cdot A(0)$. Absorbed doses to lymph nodes have been calculated for different weights of the nodes and the results are given in Fig 2 B.

Fig 2 B. The absorbed doses to individual lymph nodes with the weights 0.2, 0.4 and 0.8 grammes when the uptake of injected activity is 0.1 %.



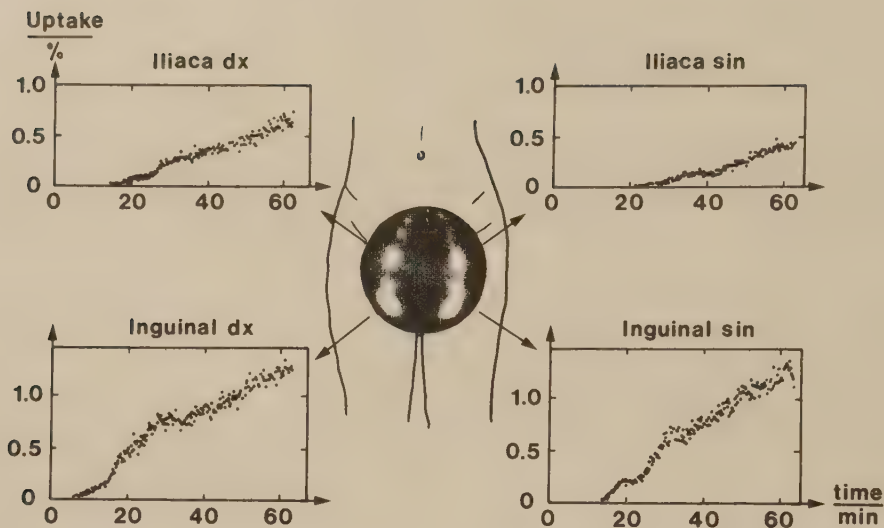
RESULTS

In Vivo Measurements

In Fig 3 an example is given of a dynamic study of the activity uptake in the iliacal and inguinal lymph nodes after injection into the back of the foot. As can be seen, the activity uptake in the inguinal nodes starts somewhat earlier than in the iliacal lymph nodes due to the distance from the injection site. In this patient the uptake on the right side appeared more rapidly than on the left side.

The scintillation camera measurements of the activity content in different node regions are given in Table II. As can be seen, the variation of activity uptake is great and ranges up to 5 % of the injected activity. The great differences are explained by the variation in injection sites and associated differences in lymph flow. Pathological conditions of the patients may also have an influence. The remaining activity in the injection sites ranges from 80 to 100 % after about five hours.

The activity uptake in the inguinal and iliacal nodes lies between 0.2 and 2.4 % of the injected activity, whereas in the axillary nodes as much as 4.4 % was detected in one



Colloid uptake in lymph nodes

Fig 3. Time activity curves of the inguinal and iliacal lymph nodes. The more rapid uptake in the inguinal lymph nodes is due to the shorter distance to the injection site.

Activity in injection site and lymph nodes (%)

Patient no	Time after injection (hours)	Injection site(s) dx sin		Lymph nodes			
				Inguinal dx sin		Iliaca dx sin	
Melanomas of extremities							
4	4.5	81	86 ^{xx})	1.3	1.5 ^{xx})	1.5	1.8 ^{xx})
6	6.5	x)	x)	0.5	1.5 ^{xx})	0.3	1.0 ^{xx})
7	5.5	99 ^{xx})	88	0.2 ^{xx})	0.5	0.3 ^{xx})	1.4
9	6.5	91	82 ^{xx})	1.0	2.4 ^{xx})	0.4	1.8 ^{xx})
Melanomas of trunk				Various nodes		Axilla dx sin	
2	4.5	99		x)		x)	0.03
2 ^{xx})	4.0	78		1.3, 1.6		4.4	x)
3	6.0	95		x)		x)	0.005
3 ^{xx})	4.5	95		0.17		0.15	x)
5	4.5	94		0.04		0.05	0.03
8	6.0	90	98	0.02, 0.11		0.2	0.05 ^{xx})

x) Not measured or undetectable

xx) Control on contralateral side

Table II. Measured activity from scintillation camera images.

patient. In lymph nodes situated elsewhere as much as 1.6 % was detected in one case.

These measurements with the scintillation camera give the total activity content in all the regional lymph nodes examined, because individual lymph nodes cannot be resolved with the parallel hole collimator.

In Vitro Measurements

There was no significant activity (< 0.001 %) in any of the metastatic lymph nodes and in 28 % of the benign lymph nodes. In the remaining benign lymph nodes the most probable activity content was 0.001 - 0.01 % in 30 % and 0.01 - 0.1 % in 33 % of the nodes. The activity content rarely exceeds 0.1 %, and only 9 % of the benign nodes had an activity content between 0.1 - 1 %. The mean weight of the 69 lymph nodes was $0.7 \text{ g} \pm 0.6 \text{ g}$ ($\pm$ S.D.).

Measured Lymph Node Depths

In order to calculate the real activity content in the lymph nodes in vivo, the depths of the nodes had to be estimated. The depths calculated with the anterior-posterior method and/or measured directly in images of lateral views show that the nodes may lie at a depth of 1 to as much as 8 cm in the body. For the depth of 8 cm a correction factor for the tissue attenuation of 3.1 must be used since the effective attenuation coefficient for the 140 keV photons is 0.140 cm^{-1} for the scintillation camera with the parallel hole collimator.

The measurements of the depths show that for a proper calculation of the activity content in the lymph nodes an estimation of the tissue attenuation must be made.

In the present investigation the thickness of the patients has been determined from lateral views with markers on the patient. For a more accurate determination, however, a transmission measurement must be performed (13). Measurements have been performed with small sources simulating lymph nodes in water phantoms and these show that the anterior-posterior method gives a very accurate estimation of the lymph node depths if the water-equivalent thickness is known. One way of determining this thickness in patients is to use a ^{57}Co -flood source. Three images must then be taken, first with the source under the patient, then with the patient alone, and finally with only the source under the camera. The water-equivalent thickness will be known from an attenuation curve (13) if the second image is subtracted from the first and then divided with the third image.

Absorbed Doses

The absorbed doses to the injection site and the individual lymph nodes are given in Fig 2 A and 2 B. For the injection site the absorbed dose varies from 170 to 40 rad per mCi (45.9 to 10.8 mGy per MBq) with all the activity remaining in the injection site and from 120 to 25 rad per mCi (32.4 to 6.8 mGy per MBq) with a biological outflow of 0.045 h^{-1} if the volume of the injection site varies from 2 to 10 ml. The absorbed dose is thus strongly reduced when the volume of injected activity is increased.

From the measurements of the actual injection volumes in the patients the mean volume was calculated to be $6.4 \pm 5.0 \text{ cm}^3$ ($\pm$ S.D.), giving an absorbed dose to the injection site of 55 rad per mCi or 40 rad per mCi with an outflow of 0.045 h^{-1} (or 14.9 and 10.8 mGy per MBq respectively).

The absorbed doses to individual lymph nodes with an assumed activity uptake of 0.1 % are given in Fig 2 B when the lymph node weight is 0.2, 0.4 or 0.8 g. With a weight of 0.8 the absorbed dose will be about 0.6 rad per mCi (0.16 mGy per MBq) of injected activity.

The absorbed dose to the gonads is shown both from the MIRD and the computer calculations to be between 10 to 15 mrad per mCi $^{99}\text{Tc}^{\text{m}}$ (2.7 to 4.1 μGy per MBq) injected on the abdomen and 0.7 mrad per mCi $^{99}\text{Tc}^{\text{m}}$ (0.19 μGy per MBq) when injected into the foot.

Correlation with Histopathology

A total of 74 lymph nodes were dissected from the specimens from five patients, and all these lymph nodes were measured for radioactivity and examined by light microscopy. Tumor growth was found in 5/74 lymph nodes. Activity uptake was detected in none of the lymph nodes infiltrated with melanoma, but in 50 of the benign lymph nodes.

Clinical Investigations

In Table I the diagnosis of the patients and the injection site are given together with the observed direction of the lymph flow. The drainage of the $^{99}\text{Tc}^{\text{m}}$ colloid from the injection site to regional lymph nodes was shown in all nine patients. In two of the five patients with trunk melanoma the images demonstrated lymph flow to more than one group of regional lymph nodes. Most of the uptake of activity in lymph nodes could be seen within the first 15 min. In one patient (no 2) with trunk melanoma a lymph node was visualized on the control side 15 cm below the axilla (Fig 4 A). This lymph node corresponded well to a previously excised

lymph node metastasis on the affected side.

A normal lymphoscintigraphy of the inguinal and iliacal lymph nodes is shown in Fig 4 B. The images show a good symmetry without any differences between the sides in uptake or uptake rate of activity.

In patients no 4, 6 and 9 with melanoma of the lower extremities a reduced uptake was found in the affected side in comparison with the control side. This was correlated to the histopathological findings of metastatic tumors in the dissected lymph nodes from patient no 6, while only benign lymph nodes were found in patients no 4 and 9. The pathological lymphoscintigraphy of patient no 6 is shown in Fig 4 C.

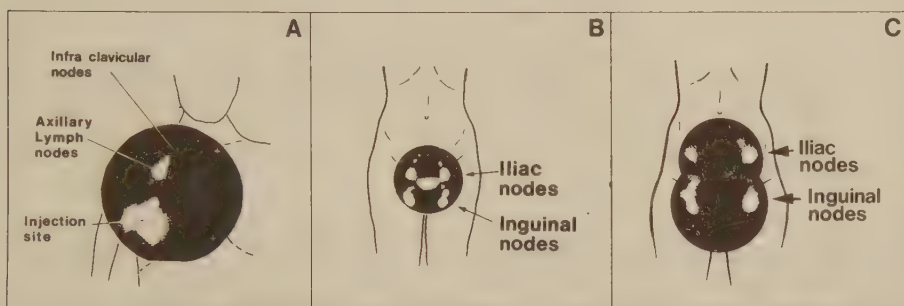


Fig 4 A. Uptake in a lymph node on the thoracic wall below the axillary nodes. The whole lymph node chain up to the infraclavicular lymph node is well visualized.

Fig 4 B. Normal activity uptake with no difference contralaterally.

Fig 4 C. Pathological activity uptake with more rapid uptake in metastatic side whereas the total uptake after 5 hours shows reduced uptake in metastatic side.

The results of the dynamic studies of the four patients with melanoma of the lower extremities are given in Table III. They show that the lymph flow was more rapid on the affected side of three of the patients.

Patient No.	Time for activity appearance (min)				Percentage uptake in lymph nodes after 100 min (%)			
	inguinal		iliaca		inguinal		iliaca	
	dx	sin	dx	sin	dx	sin	dx	sin
4	5	15 ^{*)}	15	24 ^{*)}	1.3	1.3 ^{*)}	0.7	0.4 ^{*)} ***)
6	27	30 ^{*)}	**)	**)	0.2	0.1 ^{*)}	**)	**)
7	10 ^{*)}	<10	10 ^{*)}	<10	0.1 ^{*)}	0.3	0.1 ^{*)}	0.4
9	15	<15 ^{*)}	15	<15 ^{*)}	0.3	0.9 ^{*)}	0.1	0.3 ^{*)}

*) control side

***) not measured

***) 60 min after injection

Table III. Dynamic studies of patients with melanoma of the lower extremities.

DISCUSSION

The present study shows that it is possible to register the lymph flow and the uptake of the $^{99}\text{Tc}^{\text{m}}\text{Sb}_2\text{S}_3$ -colloid in the lymph nodes with a simple scintillation camera technique when different injection sites are used. Pathological findings can easily be detected when the contralateral side is used as a control.

With a proper calibration of a camera and with a depth localization of the lymph nodes the real activity content in the lymph nodes can be estimated (13).

The absorbed dose to the injection site will be about 50 rad per mCi (13.5 mGy per MBq). This dose, however, is limited to a small volume and just outside the injected volume the absorbed dose will be extremely reduced due to the short range of the electrons. In the patient with trunk melanoma, the injection site around the scar is removed when the extended resection is performed.

To individual lymph nodes about 0.6 rad per mCi $^{99}\text{Tc}^{\text{m}}$ (0.16 mGy per MBq) can maximally be expected. The absorbed dose in the whole body will be at maximum about 15 mrad per mCi and the absorbed dose to the gonads at maximum about 70 mrad per mCi $^{99}\text{Tc}^{\text{m}}$ (4.1 and 18.1 μGy per MBq).

There is a great deal of controversy about the optimal treatment of malignant melanoma. One is whether or not to perform

prophylactical lymph node dissections in high-risk patients without clinically involved regional lymph nodes. Non-randomized trials favour elective node dissections, but randomized trials show no differences (17, 18, 19, 20). In a recent prospective randomized study no significant differences could be found between patients operated on prophylactically or when enlarged lymph nodes were diagnosed (19). This study could be criticized as the women to men ratio was nearly 5:1 and the primary melanoma tumors were localized in the distal part of the lower extremities. The result may be another in patients with trunk melanoma localized so that the lymph flow runs to more than one group of regional lymph nodes. The preliminary results from such a prospective randomized study in trunk melanoma have, however, not shown that this has any beneficial effect (20). In this study, patients with melanoma localized to the mid-trunk or in the area of the regional lymph nodes were excluded. Even if surgical removal of regional lymph nodes did not have a therapeutic effect, it reveals those patients who have occult metastases. The lymph node dissection is then to be considered as a staging procedure and patients with lymph node metastases can be subjected to adjuvant chemotherapy and/or immunotherapy (21).

A diagnostic procedure which can detect subclinical node metastases will reduce the need for surgery. Prophylactic lymph node dissection is then necessary only in a restricted number of patients with a high probability of lymph node metastases. Lymphography has been evaluated in patients with malignant melanoma. In one study false negative and false positive diagnoses were so common with this method that its value for guiding clinical decisions on patient management was nil (22). In another study the accuracy between lymphography and histopathology was good, however, the evaluation was carried out separately for the different parts of the removed lymph node chains from each patient, so therefore no reliable information for the clinical judgment was given (23).

Lymphoscintigraphy easily images the lymph flow from the primary tumor site to regional lymph nodes in melanoma patients (24, 25), but its value for this purpose has not yet been estimated. Even if the question about prophylactic lymph node dissection is still unanswered, lymphoscintigraphy can predict in which regional group of lymph nodes metastases from malignant melanoma might be found. This information is important if a staging procedure is to be performed. During the clinical follow-up it is also important to know which group of lymph nodes has the highest probability of developing recurrent disease.

In the present series, two out of five patients with trunk melanoma had lymph flow to more than one group of regional

lymph nodes (Table I). In trunk melanoma the beneficial effect is obvious to the surgeon, who has to make the decision of lymph node dissection.

In five of our patients the lymph nodes were individually dissected and measured for radioactivity and then histopathologically examined. Three patients had reduced activity uptake in the affected side in vivo compared with the control side. This reduction of the activity uptake was correlated to the histopathological findings of massive metastatic tumors in the lymph nodes from patient no 6 (Table I, Fig 4 B).

The activity uptake in benign lymph nodes had an activity uptake which was much better than with $^{99}\text{Tc}^{\text{m}}$ -labelled sulphur colloid (6). The visualization of lymph nodes in vivo with antimony sulphide colloid has been shown to be much better than with stannous phytate colloid (25, 26). The high activity uptake shown in Table II enables us to obtain excellent images within less than 5 min. The good activity uptake is related to the particle size of the antimony sulphide colloid (8).

The good qualities of antimony sulphide colloid are important when the distance to the lymph drainage is long. As a result of the dynamic studies in four patients with lower leg melanoma (Table III) it was found that the lymph flow was more rapid on the tumor side. This might be explained by the fact that the phagocytic activity had increased after the primary excision of the tumor after which the lymph flow increased.

An investigation of all patients with malignant melanoma at our hospital has now been undertaken in order to find a more accurate base for differentiating between stage I and II melanoma by means of lymphoscintigraphy.

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INTRACRANIAL METASTASES OF MALIGNANT MELANOMA TREATED BY
SURGERY.

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Intracranial metastases of malignant melanoma

ABSTRACT

In 25 patients with intracranial metastases from malignant melanoma the metastases were extirpated in all patients. Two patients had a second operation after six and ten months because of tumor recurrence. Single brain metastases were found in 20 and multiple in five patients. The interval between the primary tumor and of the intracranial metastases varied from 17 years - six months. Three patients died in complications to the surgery. The median survival time was five months (mean survival ten months). Complete relief of symptoms was observed in 17 and partial in two patients. The quality of life was improved in 17 patients and 14 of them went back to their ordinary occupation. The indications for neurosurgery are restricted in patients with extracranial or with multiple intracranial metastases.

The prognosis for patients with metastatic malignant melanoma has not improved during recent years despite attempt with a multidisciplinary approach including the newest chemotherapeutic drugs. The treatment chosen for brain metastases usually depends on the extent and localization of the brain tumors as well as the total tumor burden. In an attempt to attack the disease of malignant melanoma in a more aggressive manner using different modalities of treatment such as regional hyperthermic perfusion and palliative chemotherapy etc, the brain surgery for cerebral metastases was also included.

The aim of the present study was to analyse in retrospect the results of surgical treatment of intracranial metastases and based on these to establish realistic indications for neurosurgery.

MATERIAL AND METHODS

In 1968-1978 25 patients (15 men and 10 women, age range 31-75 years) with intracranial metastases of malignant melanoma were operated at the Department of Neurosurgery, University of Lund, Sweden. The course for these patients has been evaluated. In all patients the metastases have been proved histologically to be malignant melanoma,

The primary tumor was recognized in 18 patients, 16 before and two after the brain surgery. The period between the diagnosis of the primary tumors and of the intracranial tumors varied from 17 years - six months before the intracranial surgery. In six of the patients this interval was more than five years. At the time for the diagnosis of the intracranial metastases seven patients had extracranial tumor manifestation. Eight patients had earlier been treated for melanoma metastases localized elsewhere and were without signs of extracranial tumor.

Carotid angiography was performed in all the 25 patients, radionuclide scan in 21 and computerized axial tomography (CAT) in four patients. The intracranial tumors were localized by the angiography in all patients, by radionuclide scan in 20/21 and by CAT scan in all four patients.

Craniotomy was performed and the metastases extirpated in all 25 patients, in one of them in combination with a Spitz-Holter shunt. Two patients had a second craniotomy six and ten months after the first because of intracranial tumor recurrence. Single metastases were found in 20 and multiple in five patients. The location of the metastases was most frequently to the parietal lobes without any preference for either hemisphere (Table I). The appearance of the tumor was brown, red or dark-grey and the tumor was encapsulated in all

cases. Intratumoral haemorrhage was seen in four of the patients. The surgeon judged that all preoperatively or peroperatively diagnosed tumors were completely extirpated in all cases with single brain metastases.

Tumor location	Single tumor	Multiple tumors
Frontal lobe	4	2
Temporal lobe	3	1
Parietal lobe	10	3
Occipital lobe	2	2
Cerebellar lobe	1	1

Table I. The intracranial location of the metastases.

In connection with the brain surgery all patients received corticosteroids. Chemotherapy was given to two patients immediately before and to two patients immediately after the brain surgery because of extracranial tumor manifestations. One patient was given whole brain irradiation postoperatively.

RESULTS

The one month mortality comprises seven patients. This figure includes three patients dying from postoperative complications and four patients dying from tumor progress with continued deterioration of the cerebral symptoms (Table II). These four patients had all multiple brain tumors.

The median survival time of all patients was five months (mean survival time ten months). When the one month mortality was deducted the median survival time was six months (mean survival time 13 months). Four of these patients are still alive without signs of recurrent disease after 11, 21, 45 and 74 months respectively. One patient is still alive after 12 months with extracranial recurrence. The remaining patients are dead (Table II).

Among the six patients with a long interval between primary melanoma tumor and cerebral metastases there were three patients who survived more than one year.

All except one patient with multiple brain metastases at the operation were dead within one month. This patient sur-

vived approximately five months and was without neurological symptoms for two months. The median survival time of seven patients with concomitant extracranial metastases was one month (mean survival 2.5 months). This should be compared with a five months median survival (mean survival 15 months) for patients without synchronous metastases outside the brain. There was no difference in survival between patients with extracranial metastases treated earlier and those with no metastases. Patients with an unknown or known primary tumor had the same survival.

Patient Sex	Age (years)	Relief of symptoms	Duration (days)	Survival (days)	Cause of death
Male	53	No	-	6	Postoperative hematoma
Female ¹	43	No	-	13	Cerebral tumor progress
Female	75	No	-	23	Pulmonary embolus
Female	54	No	-	30	Cerebral tumor progress
Male	56	No	-	30	Cerebral tumor progress
Female	73	No	-	61	Cerebral tumor progress
Male	69	(Yes)	83	97	Cerebral tumor progress
Male	51	(Yes)	60	126	Cerebral tumor progress
Male	64	Yes	10	10	Septicemia
Male	57	Yes	24	24	Cerebral tumor progress
Male	53	Yes	88	105	Cerebral tumor progress
Male	41	Yes	52	141	Cerebral tumor progress
Male	57	Yes	75	146	Cerebral tumor progress
Male	52	Yes	42	180	Cerebral tumor progress
Female	39	Yes	168	187	Cerebral tumor progress
Female	53	Yes	50	240	Cerebral tumor progress
Male	51	Yes	345	345	Alive
Female	31	Yes	360	360	Alive
Male ²	74	Yes	300	396	Cerebral tumor progress
"	"	"	30	"	"
Female ²	60	Yes	220	442	Cerebral tumor progress
"	"	"	"	"	"
Male	54	Yes	486	526	Cerebral tumor progress
Female	34	Yes	633	633	Alive
Female	58	Yes	840	862	Cerebral tumor progress
Male	32	Yes	1 335	1 335	Alive
Male	45	Yes	2 220	2 220	Alive

¹Extirpation + Spitz-Holter shunt

²Operated twice

Table II. The effect on symptoms and survival after the surgical extirpation of intracranial metastases of malignant melanoma.

An immediate postoperative improvement with a relief of symptoms was seen in 19 patients, complete in 17 and partial in two (Table II). The median duration time of this clinical improvement (the one month mortality deducted) was five months (mean time 12 months) and a median survival time of these patients of six months (mean survival time 15 months). The two patients operated on a second time had complete relief of symptoms also on this occasion.

The quality of life of all patients surviving one month was evaluated. Seventeen patients had the same or improved quality of life after surgery as before. Fourteen of them went back to their ordinary occupation.

Complications

One patient had septicemia and one had a wound abscess. The patient with septicemia died postoperatively. Two patients had postoperative intracerebral hematoma, one of them died in this complication while the other was reoperated successfully. One patient died in pulmonary embolus.

DISCUSSION

The occurrence of unknown primary tumors in malignant melanoma is well known and the incidence is about 4-15 % (6). About one third of our patients had unknown primary melanoma tumors. These patients were evidently operated without any suspicion of a melanoma tumor but rather a primary cerebral tumor. Primary malignant melanoma of the central nervous system is rare (4). Criteria for primary cerebral melanoma tumors have been established by Hayward et al (8). The seven patients in the present series did not fulfil these criteria for being a primary cerebral melanoma tumor. No difference is known between primary and secondary cerebral melanoma regarding treatment and prognosis.

There are no typical neurological manifestations from cerebral melanoma metastases. The initial evidence of the metastases is usually neurological signs or symptoms as those seen in other brain tumors. Intracranial haemorrhage, subarachnoid or intracerebral is not uncommon as the first appearance of intracranial melanoma metastases (2, 5, 11, 15). The intratumoral haemorrhage may occur spontaneously or be related to chemotherapeutic treatment. It has been suggested that intratumoral haemorrhage is most commonly related to systemic chemotherapy but it is difficult to document this concept. Judged by the appearance of the metastases at surgery intratumoral haemorrhage can be misjudged because of the consistency and colour of the tumor. Usually the brain tumors are not diagnosed before they become clinically overt. Regular follow-up with for example, CAT scan

will perhaps give a greater chance of revealing asymptomatic brain metastases.

Predominantly the brain metastases occur in the distribution of the middle cerebral artery without any preponderance for either hemisphere. This may be related to the laminar blood flow or the mass of the brain being supplied by this artery (10).

The greatest chance for neurological improvement and prolonged survival is given by surgical treatment. Patients offered surgery have usually only a single tumor visualized by the preoperative examination of the brain. A favourable factor for surgery is a long interval between the treatment of the primary tumor and the occurrence of the intracranial metastases (1, 16). In our series such a correlation could also be registered.

Surgical extirpation of the metastases gives a far longer survival and a much better improvement of neurological manifestations than non-surgical treatment. The median survival of different surgically treated series is six months (1, 5, 7, 8). Our results agree with this figure. All the four patients dying postoperatively in cerebral tumor progress belonged to the non-favourable group, with multiple intracranial tumors and a short interval between primary melanoma tumor and cerebral metastases. Others have also shown that concomitant extracranial metastases have influence on prognosis and survival (1).

In our material there are seven patients with a survival of more than one year. Three patients have survived approximately two, four and six years respectively after the brain operation and are still alive in a stationary good state (Table II). A few similar or better cases of long term survival have been reported (2, 13, 19).

Non-surgical treatment such as irradiation, chemotherapy and corticosteroids alone or in combination has a minimal effect on metastatic melanoma of the brain (1, 3, 5, 6, 7, 9). Chemotherapy alone or together with corticosteroids offers minimal improvement of neurological manifestations (5). The effect of corticosteroids alone is probably quite sufficient (1, 14).

Although our results as well as those of others are not that overwhelming the poor outcome for patients with intracranial metastases justifies an aggressive attitude with surgery. The indications for neurosurgery in patients with extracranial metastases or with multiple intracranial metastases are restricted. The facts which have been established by others are further underlined in this analysis.

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the most sensitive and specific for the metabolite (Rorsman et al 1973). Exposure to sunlight leads to increased urinary levels of 5-S-cysteinyl-dopa which limits its usefulness in predicting melanoma metastases (Rorsman et al 1976, Nixon 1978). Therefore 5-S-cysteinyl-dopa determinations cannot be performed during the period from the beginning of May to the end of August in Sweden. Before 5-S-cysteinyl-dopa will be used in other countries detailed analyses of normal variations in the population have to be performed with special reference to latitude and climate.

5-S-cysteinyl-dopa cannot be used for the diagnosis of primary melanoma (clinical stage I), since the excretion values are then within normal values. A decrease of normal values can be observed after surgical removal of the primary melanoma (Agrup et al 1975). There is a sex difference regarding the urinary excretion of 5-S-cysteinyl-dopa in healthy human beings where men have higher values than women (Agrup et al 1975). This was also found in patients with melanoma metastases (I). The same condition is valid for melanoma patients without metastases. It is tempting to speculate that the same factors that make the melanoma less malignant in women may also be of importance in regulating the 5-S-cysteinyl-dopa production and excretion. One limitation of the 5-S-cysteinyl-dopa test is that some patients with malignant melanoma metastases have normal urinary excretion (I). As the 5-S-cysteinyl-dopa excretion reflects the pigment formation of the melanocytes, the metastases of these patients can be supposed to be amelanotic or hypomelanotic. In the present series about half of 19 patients with metastases and normal 5-S-cysteinyl-dopa excretion had non-pigmented metastases. Since this study was performed one patient with non-pigmented metastases had ten-fold 5-S-cysteinyl-dopa values (Agrup 1979). An important observation in the present series was that 23 patients with increased urinary levels of 5-S-cysteinyl-dopa had no metastases but later on developed manifest tumors (0.5-14 months) (I). The fact that borderline values occurred in 12 out of these 23 patients emphasizes the significance of even a minor increase in the 5-S-cysteinyl-dopa excretion. This means that the reference limit used may be changed to increase the sensitivity of the test furthermore. Repeated individual determinations are of greatest importance and each patient must be his own control.

When evaluating the effect of adjuvant and palliative therapy a careful work-up of patients is important in order to register either tumor regress or tumor progress. The methods routinely used to determine tumor progress in melanoma patients such as laboratory tests, chest X-ray, liver scintigraphy and brain scintigraphy are not as good as the estimation of 5-S-cysteinyl-dopa excretion in the urine (II). When 5-S-cysteinyl-dopa indicates tumor recurrence it is mandatory to try to find the metastases by other diagnostic methods and to have the recurrence biopsy verified (VI). A biopsy verified diagnosis is not only necessary to establish tumor recurrence during follow-up of treatment, but even before treatment of the recurrence is started. A lung lesion visualized on a chest X-ray in melanoma patients need not to be a melanoma metastasis (Cahan et al 1978). Changes on liver scintigraphy caused by benign di-

seases, e.g., gallbladder disease, can also be mistaken for melanoma metastases. The fine needle biopsy technique is suitable for verifying the diagnosis in such cases (VI). If there are suspected changes on liver scintigraphy the fine needle biopsy should be performed guided by ultrasonography or computer tomography. The postulation that fine needle biopsy should be used with restriction in melanoma patients, as seeding of tumor cells along the needle tract may occur more frequently than in other malignant tumors should not prevent its use for verifying a suspect melanoma metastasis when pathological findings are demonstrated by chest X-ray, liver scintigraphy or any other diagnostic procedure.

The measurements of urine metabolites from the melanine synthesis are useful indicators of the effects of instituted therapy, and of special interest for this purpose is the 5-S-cysteinyldopa, as it is quantitatively the most important specific product of the melanine forming cell so far known (II). Homovanillic acid which is a less specific melanine metabolite than 5-S-cysteinyldopa has been used in a small series of patients treated with dacarbazin to explore the effects of the therapy (Morgan et al 1976). There was a tendency for the urinary levels of the HVA to decrease and reach normal values during therapy even if there was tumor progress. It was thought that the dacarbazin interfered with the melanine synthesis, so the tumor became amelanotic. In the present study of dacarbazin therapy explored by 5-S-cysteinyldopa determinations the changes of the urinary 5-S-cysteinyldopa excretion were parallel to the tumor response (II). In more than half of the patients (11 out of 17 patients) there was an increased 5-S-cysteinyldopa excretion from 0.5-7 months (median time 2 months) before the metastases were detected by standard methods. In the only patient with complete tumor regression, the pathological values of 5-S-cysteinyldopa were normalized within 2 months. The favourable value of 5-S-cysteinyldopa determination is best observed in the group of patients judged to have stable disease (II). Four of six such patients should be classified as having progressive disease when the therapeutical effects were explored by 5-S-cysteinyldopa excretion. The diagnostic gain could probably be further increased and safer if the 5-S-cysteinyldopa test was performed at shorter intervals. If it can be shown that the response rate to chemotherapy is significantly lower than what is established today that kind of therapy really can be questioned.

Treatment of metastatic malignant melanoma.

Treatment modalities available for metastatic malignant melanoma are surgery, regional or systemic chemotherapy, immunotherapy, radiotherapy, hyperthermic therapy (Hersh et al 1979). Because of the limited effects of these methods of treatment when used separately, a combined approach often is necessary to attain better results. No permanent cure is possible, but combined modalities of treatment can give palliation with a prolonged survival for some patients. When different types of treatment are combined they can be given simultaneously, sequentially or both. This approach is possible for treating both occult malignant melanoma as well as clinically overt melanoma localized regionally or systemically.

Surgery is the basic treatment of both primary melanoma and metastatic

melanoma, but plays a limited role in patients with systemic metastases (Goldman 1975, Rosenberg 1976, Patterson 1979, Veronesi and Cascinelli 1979). As discussed before (vide supra) there is contention about lymph node dissection for patients with suspected occult lymph node metastases (Goldsmith et al 1970, McCarthy et al 1974, Southwick 1976, DasGupta 1976, Holmes et al 1977, Fortner et al 1977, Veronesi et al 1977, Sim et al 1978, Veronesi and Cascinelli 1979). Several non-randomized trials favour lymph node dissections, but the only two reported randomized trials show no differences (Veronesi et al 1977, Sim et al 1978). One of these randomized studies can be criticized because of a woman to man ratio of about 5:1, the primary tumors were mainly localized to the distal part of the lower extremities and more than half of the patients were without exact microstaging of the primary tumor (Veronesi et al 1977). In the other study patients with melanoma localized to the midtrunk or in the area of the regional lymph nodes were excluded (Sim et al 1978). Therefore clinicians managing melanoma patients have to judge from their own experience what treatment is suitable for high risk primary melanoma (Clark IV-V, Breslow > 2.25 mm) or include their patients in studies which will further explore the value of prophylactic lymph node dissection. If surgery is without any therapeutic effect lymph node dissection can be considered as a staging procedure, which will direct other treatments. Considering the morbidity of lymph node dissection (Harris et al 1973, McCarthy et al 1974, Holmes et al 1977) there is an urgent need for non-invasive methods suitable for staging the patients (IV).

Another problem is whether the lymph node dissection should be performed in continuity with the primary tumor or not. Fortner et al (1975) have expressed that discontinued dissection increases the frequency of regional in transit metastases, but this is not accepted by others (Veronesi and Cascinelli 1979). To avoid the increased frequency of in transit metastases some authors perform elective lymph node dissections four to six weeks after the excision of the primary tumor. Sim et al (1978) included such a group of patients in their prospective randomized study on prophylactic lymph node dissection. No difference was observed regarding the occurrence of in transit metastases in that study. An alternative approach to this problem is the use of isolated regional hyperthermic perfusion. By perfusion treatment micrometastases which are supposed to occur along the lymph pathways from the primary tumor site to regional lymph nodes, may be irradiated. Regional hyperthermic perfusion has an effect on manifest regional in transit metastases (V). Whether regional hyperthermic perfusion therapy contributes to a lower frequency of local recurrences when used as an adjuvant to surgical treatment of primary melanoma has not been established in any controlled study, but compared with historical controls treated conventionally some authors suggest improved results (Stehlin et al 1975, Sugarbaker and McBride 1976, Schraffordt-Koops et al 1977, Golomb et al 1979, Rege et al 1979).

In some patients with symptoms or complications from distant metastases, there are indications for surgical excision of the metastases (III) (May and Edwards 1976, Amer et al 1978, Bremer et al 1978, van Dongen and van Slooten 1980, Dahlbäck et al 1980). It is important that these patients are carefully evaluated to establish if subclinical metastases

are occurring elsewhere at the same time. The possibility of using other methods of treatment to control the metastases has also to be considered. The main indication for surgery of lung metastases and cerebral metastases is based on the occurrence of clinical symptoms, the localization of the metastases, the tumor-free interval, tumor-doubling time and whether single or multiple metastases are occurring (III) (Amer et al 1978, van Dongen and van Slooten 1978). Depending on the localization of the tumor, patients with symptoms making them completely or partially disable may be considered for surgery as an exception, even if the prognosis seems poor (III). Long-term survival has been reported particularly in patients with cerebral metastases (III) (McCann et al 1968, McNeel and Leavens 1968, Amer et al 1978).

The incidence of cerebral metastases from malignant melanoma has increased during the last decades (Budman et al 1978). This may reflect a more aggressive therapy with surgery and chemotherapy for extracerebral metastases, which does not influence the cerebral tumors. At autopsy approximately three fourths of the melanoma patients have cerebral metastases, but only half of these patients die as an immediate course of the brain tumor (Budman et al 1978). Primary melanoma of the central nervous system is rare (Bergdahl et al 1972). No difference is known regarding treatment and prognosis between the primary and secondary cerebral melanoma. Usually brain metastases from malignant melanoma are not diagnosed before they become symptomatic (III). The neurological signs and/or symptoms are the same as those observed in connection with other brain tumors. It seems that the greatest chance of revealing asymptomatic brain metastases from malignant melanoma will be if a regular follow-up including 5-S-cysteinyldopa (I, II) is complemented with computer tomography of the brain when increased urinary values of 5-S-cysteinyldopa are found. The brain scintigraphy is probably not sensitive enough to detect subclinical brain metastases. In a small series of patients with malignant melanoma and with symptoms from the central nervous system, metastases were more often diagnosed by the computer tomography than the brain scintigraphy (Cronqvist 1980).

Surgery offers the best possibilities for palliation in patients with cerebral melanoma (III). From the present series of 25 patients operated on with brain surgery the median survival time was 6 months, when the one month mortality was deducted. Seven of these patients survived more than one year and four patients are still alive in a stationary good condition two, four and six years after the brain surgery. Similar results of long-term survival have been reported by others (McCann et al 1968, McNeel and Leavens 1968). More important than the survival time is the condition of the patients after the operation. In our series 19 patients became asymptomatic, 17 of these had complete relief from symptoms. The duration of the asymptomatic period was median five of the six months survival. The "quality of life" was unchanged or improved for 17 patients after surgery and 14 of these patients went back to their ordinary occupations. It must be noted that the two patients who were operated on a second time because of a recurrent cerebral tumor, gained also on this occasion complete relief from symptoms. These results justify an aggressive attitude with surgery for patients with cerebral melanoma. From

this series it can be estimated that patients with single brain metastases, no extracranial disease and a long disease-free interval after treatment of the primary tumor have a favourable prognosis (III). The good results have been obtained mainly without other modalities of treatment as radiotherapy and chemotherapy. Partial relief from neurological signs and symptoms can be achieved by radiotherapy for patients with multiple cerebral metastases from malignant melanoma (Beresford 1972, Einhorn et al 1974, Amer 1978, Bremer et al 1978). As corticosteroids are used together with radiotherapy and as corticosteroids alone have a positive effect on the neurological symptoms, it is impossible to establish whether radiotherapy has any benefit at all (Ruderman and Haal 1965, Amer et al 1978). With regard to the restricted survival time in the majority of patients with surgically removed brain metastases and that no study including surgery and radiotherapy has been performed with better results such a combination treatment has to be avoided.

The radiosensitivity of malignant melanoma has been considered to be low. Nevertheless, radiotherapy has been used in both primary melanoma and in metastatic melanoma with varying results (Hellriegel 1963, Hilaris et al 1963). It has been stated that malignant melanoma may be sensitive to radiotherapy if a dose schedule with large absorbed doses at each fraction is used (Habermalz and Fischer 1976). Using such a dose schedule Habermalz and Fischer (1976) gained partial and complete tumor regression in almost all patients treated. The response rate was shown to be a function of the dose per individual treatment and not of the total dose given. In reported series of cerebral malignant melanoma treated by radiotherapy low absorbed doses have been used. The new dose schedule recommended is not suitable for irradiation of brain metastases as the large absorbed doses may have a damaging effect on the brain tissue (Phillips and Buschke 1969, Berge et al 1974). These limitations of radiotherapy indicate that brain surgery alone must be recommended.

There are extensive studies of chemotherapeutic treatment of metastatic melanoma but, most of these studies have been without success (for review see Comis and Carter 1974, Bellet et al 1979, Benjamin 1979). No single drug has given a better response rate than dacarbazin with an overall tumor response in the magnitude of 20 % in advanced malignant melanoma. Only a few of these studies have been properly controlled clinical ones. The only drugs with a response rate comparable to that of dacarbazin are the nitrosureas (Comis and Carter 1974). In malignant melanoma no chemotherapy combination shows any advantage over the single drug therapy (Bellet et al 1979, Benjamin 1979). The dacarbazin dose schedule usually used is 200-300 mg/m²/day intravenously for courses of five days at intervals of 4-6 weeks. Other dose schedules have been used with a similar tumor response rate apart from some studies (Benjamin 1979). Dacarbazin is associated with moderate toxicity, most commonly nausea and vomiting but also minor myelosuppressive effects. In the present series the most remarkable side effect observed was neurological symptoms initiated by the dacarbazin therapy in three of 17 patients (II). In a further series of 17 patients, neurological symptoms were observed in four of them. Thus 20 % of the patients treated with dacarbazin at our department presented neurological symptoms one to two weeks after start

of therapy. This figure of 20 % should be compared with that of 5 % in some earlier reports (Nathanson et al 1971, Kingra et al 1971, Ahman et al 1974). The increased excretion of 5-S-cysteinyl-dopa concomitant with neurological symptoms support the theory that the drug may have an effect on subclinical brain metastases by causing bleeding, oedema, necrosis etc (II). In patients with verified or suspected brain metastases the dacarbazine therapy ought to be questioned since this treatment may initiate or aggravate neurological symptoms for the same reason as mentioned above (Hafström and Jönsson 1980). From these observations follows that patients evaluated for systemic dacarbazine therapy because of extracerebral melanoma metastases have to be examined by computer tomography of the brain before administration of the drug. The tumor response in the present series (II) is well comparable with others. The response to systemic chemotherapy is mainly related to the localization of the metastases. Particularly good results have been achieved for patients with subcutaneous and lymph node metastases.

Regional chemotherapy can be given either by intraarterial infusion (open circuit) or by isolated perfusion (closed circuit) (II, V) (Klopp et al 1950, Creech et al 1958, Sullivan and Watkins 1965). Regional intraarterial infusion and perfusion techniques have been developed for treating tumors in several parts of the body. The goal of these techniques is to deliver a high amount of the drug into the tumor-bearing area with a minimum of systemic toxic effects. The technique for regional intraarterial infusion is well established (Klopp et al 1950, Sullivan and Watkins 1965, Virtanen 1973). The drugs are infused through a catheter placed in the artery leading to the actual region. Indications for such treatment are local tumor, in for example separate organs such as the pancreas or liver or other anatomic sites that do not permit isolated regional perfusion. In patients with contraindications for general anesthesia, which is necessary for the perfusion treatment, infusion therapy is an alternative method. The dose schedule for intraarterial infusion with dacarbazine is the same as for the systemic administration, but the courses are given at shorter intervals. In four patients treated by intraarterial infusion of dacarbazine the therapeutic results were not impressive (one patient had stable disease, three patients progressive disease)(II). The frequency of side effects, nausea and vomiting, was remarkably low compared with the systemic therapy. In contrast to our series, other authors report a positive effect to the magnitude of 41-64 % by intraarterial dacarbazine therapy (Einhorn et al 1973, Krementz et al 1979). The few reported series on melanoma patients are small and not comparable so it is impossible to establish if a better response rate is achieved when dacarbazine is administered intraarterially than intravenously. Intraarterial infusion may have a place in the therapeutic arsenal for metastatic malignant melanoma for the palliation of regional disease, alone or in combination with radiotherapy or as a complement to surgery for patients with localized disease judged to be irresectable. There is limited experience from infusion chemotherapy for patients with melanoma metastases in the liver (Einhorn 1973, Krementz et al 1979). In the present series (II) one patient with liver metastases was treated by intraarterial infusion of dacarbazine. This patient received the treatment after the temporary dearterialization of the liver had been performed,

and was judged to have stable disease for four months. However, the 5-S-cysteinyl-dopa excretion indicated tumor progress after two months. A further two patients have been treated with a temporary dearterialization and intraarterial infusion of dacarbazine. Objective tumor response for five months has been registered. Evidently it is possible to affect liver metastases by a combination of dearterialization and intraarterial dacarbazine infusion.

The technique for regional isolated perfusion has remained essentially the same since 1958 with the exception of the inclusion of hyperthermia in 1967 (Creech et al 1958, Stehlin et al 1975) (V) (Fig 2). Although isolated regional perfusion has been used in melanoma patients for more than two decades, its value has not definitely been established. A synthesis of the results from different series of patients is practically impossible because of lack of uniformity in classification of the disease extent, the performance of the perfusion treatment and of complementary surgery given. Moreover no randomized controlled studies have been reported in this field. An improved clinical course of melanoma patients treated by regional perfusion with or without heat has been documented in several studies (Stehlin et al 1975, McBride et al 1975, Weaver et al 1975, Hansson et al 1977, Schraffordt-Koops et al 1977, Tonak et al 1979, Krementz et al 1979, Stehlin et al 1979). The best results are reported by Stehlin (Stehlin et al 1975).

There are many factors to be kept in mind when discussing the regional hyperthermic perfusion technique, e.g., the rationale for using hyperthermia, the proper drugs, the importance of oxygenation and leakage. The effect of hyperthermia on malignant melanoma tumors has been verified both in vivo and in vitro. In vitro malignant melanoma cells may be more sensitive to hyperthermia (43°C) than normal melanocytes (Stehlin et al 1975). Cavaliere et al (1967) have shown that regional hyperthermic perfusion without any drug has a good tumor destructive effect on patients with malignant melanoma. There are many reasons why hyperthermia might be useful in the treatment of cancer; the tumor cells may be more sensitive to heat than normal cells, the tumor cells may be more sensitive to heat during hypoxia and/or low pH and with deficient nutrients (Field and Bleehen 1979). The enhanced tumor response when heat is combined with cytostatic agents such as melphalan may be caused by the different effects on the cell cycle. Melphalan is a radiomimetic drug. It is well-known that such drugs have no effect on the S-phase of the cell cycle, which on the contrary is sensitive to hyperthermia. It can also be speculated that hyperthermia increases the blood flow to the tumor cells, damages the cell membranes and increases the uptake of the drug in the tumor cells. A direct correlation between temperature and the binding of a cytostatic agent (Thio-Tepa) to the perfused tissue has been demonstrated (Rochlin et al 1961). Very little is known about the pharmacokinetics of melphalan at temperatures used in regional hyperthermic perfusion. In vitro there is increased hydrolysis of melphalan at temperatures above 38°C (Chang et al 1978). Further investigation in this field is necessary and now also possible as melphalan can be analysed by a high liquid chromatography method (Chang et al 1978). Systemic administration of melphalan in melanoma patients gives a low response rate (10 %) compared

with that of dacarbazin (20 %) (Comis and Carter 1974, Bellet 1979). There are no reports on the use of dacarbazin in regional hyperthermic perfusion. It has been postulated that dacarbazin has a pronounced light and heat sensitivity and therefore cannot be used. Recently in vitro investigations of dacarbazin have shown that the heat sensitivity is not very pronounced (Miles Laboratory 1979). By protecting the perfusion system from light the drug could be used for perfusion. The oxygenation of the perfusate is thought to be important for protection of the normal tissue. In addition, increased oxygen tension in the tissue may potentiate the action of melphalan (Krementz and Knudson 1961). On the other hand, it is said that hypoxia plays an important part for the rationale use of heat (Field and Bleehen 1979). The optimal oxygen tension of the perfusate is not established. Probably the oxygen tension of the perfusate does not reflect the physiological oxygen supply to the normal tissue, so it should be better to measure the oxygen tension in the venous outflow or in the tissue of the extremity.

Tissue necrosis leading to amputation seldom occurs after hyperthermic perfusion. In 13 cases out of approximately 2 000 perfusions reported in the literature, amputation of the perfused limb has been performed due to necrosis (Hafström and Jönsson 1979). After adding hyperthermia to the perfusion treatment there was an increase of complications with oedema, local burns, nerve injuries and renal failure (Stehlin 1969, Moricca et al 1977). There are many factors which can account for this, e.g., oxygen tension, hyperthermia and the drugs. The nerve injuries may be caused by a toxic effect of the combination of the drug and heat or signs of an acute compartment syndrome (Schraffordt-Koops 1972). This acute syndrome may be due to mechanical disturbances in the local circulation caused by damage to the permeability to the blood vessels from hypoxia, heat and chemotherapy. The complication rate in the present study (V) and in others is not of such a magnitude that the procedure is contraindicated in more than exceptional cases. In a regional perfusion system it is important to prevent leakage from the region to the systemic blood circulation. Leakage from iliac and from femoral perfusion is almost the same and after one hour the leakage has proved to be 10-30 %, presumably this is higher when the perfusion time is two hours (Stehlin et al 1961). To minimize leakage the perfusion pressure was kept below the mean systemic arterial pressure (V). After leakage of 62 % severe bone marrow depression was established (Stehlin et al 1960). In the present series the blood count reveal no effect on the bone marrow indicating a leakage of less magnitude (V). In a review of 2 000 perfused patients reported the myelosuppressive effect was approximately 4 % (Hafström and Jönsson 1979). To study the leakage different methods have been used such as Cr-51-tagged red cells or I-131-albumin (Stehlin et al 1961, Cox 1975, Pennington 1976). It would be of interest to measure the concentration of melphalan both in the perfusion circuit and in the general circulation. This leakage may differ from the test substances used.

Stehlin et al (1975) have suggested that the improved long-term survival of patients with local disseminated disease has to be explained by some systemic effect of the hyperthermic perfusion. The elimination of the tumor on the extremity cannot be more complete than that obtained after

amputation. By destroying a local tumor, stimulation of the immune response of the patient is received. It has been observed both clinically and experimentally that such a stimulation is present after regional hyperthermic perfusion (Stehlin et al 1975). Stehlin reported on patients with multiple lesions on the trunk which disappeared following perfusion treatment. Such an effect on the specific serum toxicity has been found in some of our patients, so therefore manifest tumor is not removed until after 4-6 weeks (V)(Jönsson et al 1977). Since the report from Creech et al (1958) there have been more than 20 publications on the results of regional perfusion, most of them presented after 1975 (Stehlin et al 1975, McBride et al 1975, Weaver et al 1975, Cox 1975, Shingleton et al 1975, Brown et al 1976, Wagner 1976, Sugarbaker and McBride 1976, Hansson et al 1977, Lejeune et al 1977, Schraffordt-Koops et al 1977, Tonak et al 1979). Of these reports, only five are on regional hyperthermic perfusion (Stehlin et al 1975, Lejeune et al 1977, Schraffordt-Koops et al 1977, Jönsson et al 1977, Tonak et al 1979) and the remaining ones concern perfusion with perfusate of body temperature. The effect of both normo- and hyperthermic perfusion on manifest tumors is well established and more than 50 % tumor regression has been reported (36-100 %) (Stehlin et al 1975, Weaver et al 1975, Hansson et al 1977, Lejeune et al 1977, Schraffordt-Koops et al 1977). In the present series such a tumor response was registered in eight out of 10 patients (V) (Fig 8 a och b).

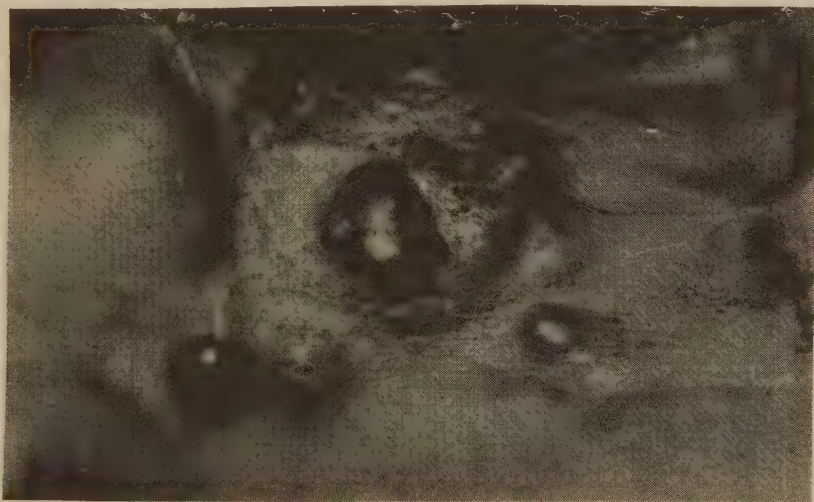
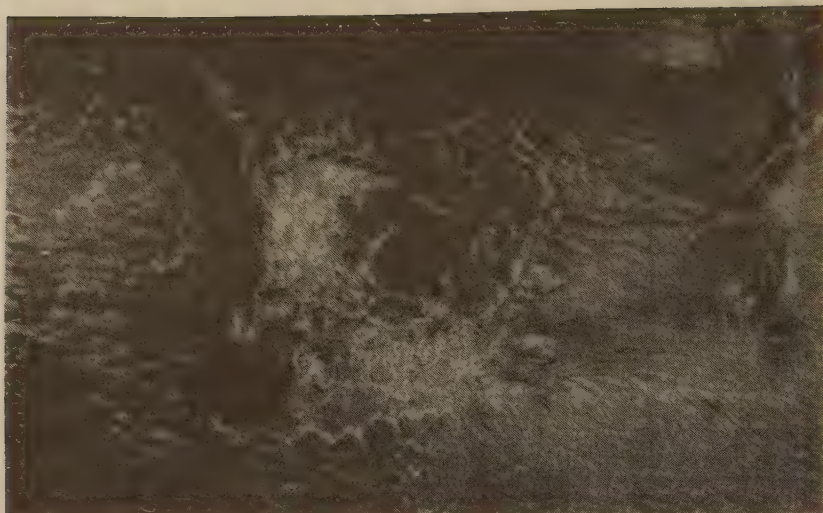


Fig 8 a.

Fig 8 a och b. A few days after the perfusion the tumor began to swell and soften and within the next seven days it shrank and dried and finally it was sloughed off. On the above picture (8 a) the state before regional hyperthermic perfusion and on the below picture (8 b) two weeks later.

Fig 8 b.



In a study of 53 patients with local recurrences and in transit metastases on the extremities Stehlin et al reported a 5-year survival rate of 52.5 % after hyperthermic perfusion (Stehlin et al 1979). In a comprehensive review of 30 patients (stage IIIA) treated with hyperthermic perfusion and 27 patients (stage IIIA) treated with surgical excision with or without normothermic perfusion, the 5-year survival was 76.7 % and 22.2 % respectively (Stehlin 1975). When comparing historical controls, corrections for different prognostic factors have been performed. Other authors have reported on a 5-year survival rate of 28-39 % after normothermic perfusion (Krementz and Ryan 1972, Shingleton et al 1975). The 2- and 3-year survival rates vary from 30-65 % in other series of regional perfusion (Weaver et al 1975, Hansson et al 1977, Schraffordt-Koops et al 1977, Golomb 1972). For a further comparison the 2-3-year survival time after major amputation varies between 15-36 %, and 20 % for patients only treated by surgical excision (Turnbull et al 1973, Fortner et al 1974, Cox 1974).

In the present series patients with the recurrence site on the thigh have a poorer prognosis than those with the recurrence on the lower part of the limb (Table V). This seems to be related to the occurrence of synchronous regional lymph node metastases. These results are in agreement with Krementz et al (1972), whose patients with regional lymph node metastases nearly all developed distant metastases after the perfusion treatment. The 5-year survival time in this series of patients varied from 17-64 % according to the extension of the regional tumors on the extremities. These results indicate that regional hyperthermic perfusion of patients with tumors localized on the proximal part of the extremities or with positive regional lymph nodes may be questioned. This illustrates the fact that knowledge of whether or not there is tumor growth in regional lymph nodes is a central point for the choice of treatment and further underlines the urgent need for the non-invasive method for diagnosing lymph node metastases. Until such a method is available, fine needle biopsy may be suitable in patients with palpable nodes, even if

they are clinically judged to be without tumors.

At any event, it would appear that regional isolated perfusion can favourably affect localized metastatic malignant melanoma and give prolonged survival to some patients, when combined with surgical excision (V). Although the results do not differ significantly from those after amputation, the regional perfusion technique is a possible means of saving the extremity for many patients.

CONCLUSION

For patients with metastatic melanoma, 5-S-cysteinyldopa excretion in urine has a prognostic value. A suitable time to determine 5-S-cysteinyldopa is in combination with the clinical examination during the follow-up before other diagnostic procedures. Repeated individual determinations are of the greatest importance. Each patient must be his own control. During chemotherapy 5-S-cysteinyldopa indicates tumor progress earlier than other diagnostic methods. This means that repeated determinations at shorter intervals may lead to altered interpretations of tumor response.

Surgery for cerebral metastases from malignant melanoma offers some patients complete relief from symptoms and improved "quality of life". Moreover, the indications for neurosurgery are restricted. Patients with single brain metastases, no extracranial disease and a long disease-free interval after treatment of the primary tumor are the most suitable candidates.

A quantitative scintillation camera technique for investigation of the lymph drainage after subcutaneous injection of Technetium-99-m-antimony sulphide colloid has been developed. This technique gives only small absorbed doses to the injection sites and the gonads. In patients with malignant melanoma of the trunk the lymph drainage can easily be visualized and prediction made as to which group of regional lymph nodes tumor cells may migrate and cause metastases. Quantitative lymphoscintigraphy may increase the possibility of detecting lymph node metastases which could be of great value as a staging procedure in patients with malignant melanoma.

Hyperthermic perfusion has an oncolytic effect on manifest malignant melanoma and gives for some patients local control of the disease with a prolonged survival time. Regional perfusion is often a possible means of saving the extremity. The results are most favourable in patients with recurrent disease localized to the lower part of the extremities and patients without tumor-involved regional lymph nodes.

Fine needle aspiration cytology is the method of choice for the establishment of a correct diagnosis of recurrent melanoma during the follow-up. This method is extremely accurate, particularly for patients with enlarged lymph nodes, and is therefore preferable to diagnostic surgical excision.

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